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ıt application number *Patent Office will fill in this part)*	31 AUG 1999 **9920558.5**
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applicant is a corporate body, give the try/state of its incorporation	ENGLAND
of the invention	METHODS FOR PARTICLE FORMATION AND THEIR PRODUCTS
e of your agent *(if you have one)*	MEWBURN ELLIS C P GREAVES & CO
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ıatement of inventorship and of right to of a patent required in support of this ɜt? *(Answer 'Yes' if:* *y applicant named in part 3 is not an inventor, or* *re is an inventor who is not named as an plicant, or* *y named applicant is a corporate body.* *te (d))*	YES

METHODS FOR PARTICLE FORMATION AND THEIR PRODUCTS

This invention relates to methods for forming particles of a substance of interest (a "target substance") using supercritical fluid antisolvents. It also relates to the products of such methods.

In particular, it relates to new applications and products of the particle formation technique known as SEDS (Solution Enhanced Dispersion by Supercritical fluids), which is described in WO-95/01221 and (in modified versions) in WO-96/00610 and WO-98/36825. It has been found that this technique may be used to produce novel products having advantageous physicochemical characteristics.

More particularly still, the present invention is concerned with multi-component products, ie, products which contain two or more target substances. It has been found that SEDS can be used to coformulate such multi-component products, especially coformulations of pharmaceutically active ingredients with polymer excipients.

It is often desirable to coformulate pharmaceuticals with "carriers" (which may be polymeric) in order to modify their solubility profiles and hence, for example, improve the dissolution of an otherwise poorly soluble drug or else slow the dissolution of a highly soluble drug so as to provide controlled release for a period of time after administration.

Techniques are already known for preparing such drug/carrier coformulations, including evaporation and coprecipitation. Such approaches are often limited however by manufacturing difficulties, including environmental constraints, solvent problems such as the need for multiple solvent systems and the consequent risk of phase separation, harvesting difficulties and the high levels of carrier often required. Another major limitation tends to be the poor physical properties and processing characteristics of the particulate products, which can be "sticky", may contain unacceptable levels of residual solvent, may suffer poor chemical and physical stability (such as a tendency for amorphous phase drugs to crystallise on storage, with consequent changes in their dissolution profiles) and are often in the form of large particles which need to be further reduced in size before they can be processed into commercial products. It is often difficult to control the morphology of the drug in the system, ie, the relative proportions of its crystalline and amorphous phases. As a result, known preparation techniques tend to have been practised largely on a laboratory, rather than a commercial, scale.

The products of the present invention are coformulations of an active substance,

The amorphous phase of the active substance in the coformulation is preferably stable e, does not change to the crystalline form) for at least three, preferably six, more preferably ine or twelve months after its preparation under suitable low temperature storage conditions.

Where the active substance is paracetamol and the polymeric material is ethyl cellulose, referably between 95 and 100% of the paracetamol is present in an amorphous form, and the aracetamol represents at least 1%, more preferably at least 2% or 5% or 10%, of the oformulation.

Where the active substance is paracetamol and the polymeric material is hydroxypropyl nethyl cellulose, preferably between 95 and 100% of the paracetamol is present in an morphous form, and the paracetamol represents at least 10%, more preferably at least 20% r 25% or 28% or 30% or 35%, of the coformulation.

Where the active substance is indomethacin and the polymeric material is ethyl cellulose, preferably between 95 and 100% of the indomethacin is present in an amorphous form, and the indomethacin represents at least 10%, more preferably at least 20% or 25% or 30% or 35%, of the coformulation.

Where the active substance is indomethacin and the polymeric material is hydroxypropyl methyl cellulose, preferably between 95 and 100% of the indomethacin is present in an amorphous form, and the indomethacin represents at least 10%, more preferably at least 20% or 25% or 30% or 35% or 40%, of the coformulation.

Where the active substance is indomethacin and the polymeric material is poly (vinyl pyrrolidone), preferably between 95 and 100% of the indomethacin is present in an amorphous form, and the indomethacin represents at least 20%, more preferably at least 25% or 30% or 40% or 50% or 60% or 65%, of the coformulation.

Where the active substance is carbamazepine and the polymeric material is ethyl cellulose, preferably between 95 and 100% of the carbamazepine is present in an amorphous form, and the carbamazepine represents at least 10%, more preferably at least 20% or 25% or 30%, of the coformulation.

Where the active substance is carbamazepine and the polymeric material is hydroxypropyl methyl cellulose, preferably between 95 and 100% of the carbamazepine is present in an amorphous form, and the carbamazepine represents at least 10%, more preferably at least 20% or 25% or 30%, of the coformulation.

Where the active substance is theophylline and the polymeric material is ethyl cellulose, preferably between 95 and 100% of the theophylline is present in an amorphous form, and the

The invention also provides a method for preparing a coformulation of indomethacin and poly (vinyl pyrrolidone), using an anti-solvent-induced particle formation process, preferably a SEDS process. The invention provides the products of such a method, and the use of a SEDS process in it.

The invention will now be described, by way of example only, with reference to the following experimental data and the accompanying figures, of which:

Figure 1 is a schematic illustration of apparatus usable to carry out methods, and obtain products, according to the invention (see the experimental example below);

Figures 2-13 are SEM (scanning electron microscope) photographs of some of the starting materials and products of the example;

Figures 14-16 show dissolution profiles for three of the systems investigated in the example, namely paracetamol:HPMC (Figure 14), theophylline:EC (Figure 15) and indomethacin:HPMC (Figure 16);

Figures 17-27 show plots of crystallinity against drug weight fraction for the systems investigated;

Figure 28 is an example DSC (differential scanning calorimetry) trace for one of the systems investigated;

Figures 29-40 are DSC traces for, respectively, crystalline indomethacin and a number of indomethacin:PVP coformulations prepared in the example;

Figures 41 and 42 are plots of $(\delta_s^d - \delta_s^p)$ against X (see Table 11 below) for some of the systems investigated; and

Figures 43 and 44 show, respectively, the structure of the γ-indomethacin polymorph and the effect of PVP upon it.

Experimental example

The following experiment investigated the use of a SEDS process to coformulate various drugs and polymers. The physicochemical characteristics of the products, in particular the degree of interaction between the two components, the proportions of the crystalline and amorphous phases of the drug, the particle size and morphology, the relative concentrations of the drug and the polymer (ie, the drug "loading") and in some cases the product stability, were tested and where possible manipulated by altering the operating conditions and other reagents (solvents) present. The relationship of the degree of drug crystallinity to the drug loading was

Material	Supplier	Grade	Lot Number
L-Ascorbic acid	Sigma	A0278	45H0296
Carbamazepine	Sigma.	C4024	28F0109
Indomethacin	Sigma .	I7378	26H0807, 67H1609
Ketoprofen	Sigma	K1751	126H1330
Paracetamol	Sigma	A7085 99.0%+	96H1124
Theophylline	Sigma	T1633 Anhyd. 99%+	107C0064
EC	Colorcon	7cps	KI10013T01
HPMC	Shinetsu	3cps (603)	55-508
PVP	Sigma	Av.Mol.Wt.10,000	116H0840
Dichloromethane	BDH	AnalaR 99.5%+	K23525480 702, K24254680 734, K24481180 745
Chloroform	BDH	AnalaR 99.0-99.4%	K25138841 817
Ethanol	BDH	AnalaR 99.7-100%	724108, 747408, 760907, 776907, 816507, 837707
Ethanol	Rathburn	HPLC	8H10JA
Methanol	BDH	AnalaR 99.8%+	K25094770 817
Sodium dihydrogen orthophosphate	Sigma	99.0%+	105H1203

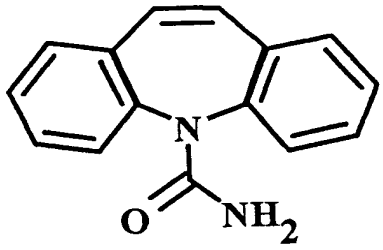
De-ionised water was obtained from a Jencons Waterstill 4000X

Suppliers

Sigma Chemical Co. - St. Louis, Missouri, USA
Shinetsu Chemical Company - Tokyo, Japan
Colorcon, Dartford, Kent, England
BDH (Merck) Poole, Dorset, England
Rathburn Chemicals Ltd, Walkerburn, Peebleshire, Scotland

Carbamazepine

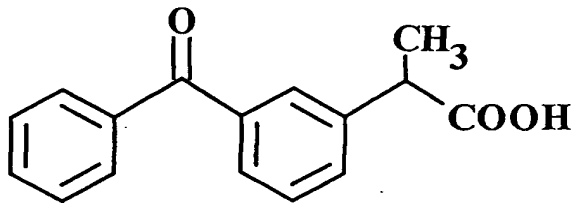
Chemical name	5*H*-Dibenz[b,f]azepine-5-carboxamide
Therapeutic Category	Analgesic, anticonvulsant
Molecular Weight	236.3
Appearance	White, crystalline
Morphology,	Crystalline, exhibits polymorphism
Melting point	190-193°C
Solubility	Soluble in ethanol, acetone, dichloromethane.
	Insoluble in water and ether



Chemical structure of carbamazepine

Ketoprofen

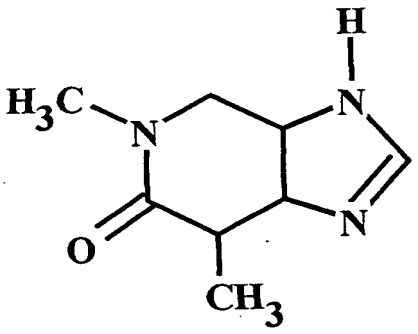
Chemical name	3-Benzoyl-a-methylbenzeneacetic acid
Therapeutic Category	Anti-inflammatory, analgesic
Molecular Weight	254.3
Appearance	White, crystalline
Morphology,	Monoclinic system, usually plates, sometimes needles
Melting point	94°C
Solubility	Soluble in ethanol, acetone, dichloromethane, dimethylformamide, ethyl acetate
	Practically insoluble in water



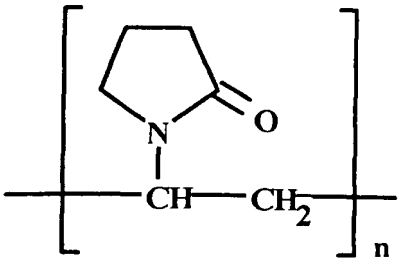
Chemical structure of ketoprofen

Theophylline

Chemical name	3,7-Dihydro-1,3-dimethyl-1H-purine-2,6-dione
Therapeutic Category	Bronchodilator
Molecular Weight	180.2
Appearance	White, crystalline
Morphology	Thin monoclinic crystals
Melting point	270-274°C (monohydrate)
Solubility	Soluble in hot water, acids, alkalis, ammonia (%). Slightly soluble in cold water (0.8%), ethanol (1.2%), chloroform (0.9%). Insoluble in ether



Chemical structure of theophylline



Chemical structure of polyvinylpyrrolidone

In Table 1, δ_d, δ_p, and δ_h are the partial solubility parameters representing dispersive, polar and hydrogen bonding effects respectively; δ_t is the total solubility parameter, where $\delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2$ [5]; δ_s is the total specific (ie, polar and hydrogen bonding) solubility parameter.

The principal operating conditions (temperature, pressure, fluid flow rates and nozzle orifice diameter) were manipulated and optimised for each drug/polymer system. Different drug:polymer concentration ratios were also tested.

It was found that temperatures in the range 34-50°C and pressures between 80 and 100 bar were preferable for processing these polymers. Anti-solvent:target solution flow rate ratios (into the particle formation vessel) were between 66:1 and 200:1, ie, an anti-solvent flow rate of 20 ml/min was used with target solution flow rates of between 0.1 and 0.3 ml/min.

Nozzle outlets of internal diameter between 200 and 500 micron were found to be more susceptible to blockages than those with 100 micron internal diameter. This was believed to be due to the fast removal of solid materials forming inside the 100 micron nozzle by the highly turbulent fluid flows within it. It was thought that a larger nozzle bore allowed material to accumulate and thus to obstruct the nozzle outlet.

The target solutions generally contained both the drug and the polymer being coformulated. Selection of a suitable solvent in each case depended on the properties of both reagents, but was particularly important for the polymer systems under study because of the potential difficulties of processing polymeric solutions and dispersions. Polymeric dispersions can exhibit very high viscosities, even when dilute. In "poor" solvents the polymer strands remain tightly packed and interactions tend to be limited. However in "good" solvents the polymer matrix will relax and loosen which allows both a greater degree of interaction and a lower viscosity, important respectively for the production of intimate drug/polymer mixtures and for the processing requirements of SEDS [1].

Of the polymers studied, HPMC is dispersible in water and in alcohol/dichloromethane mixtures, whereas EC is less polar, is not dispersible in water but can be dispersed in organic solvents such as ethanol, to an extent determined by its ethoxyl group content [2]. PVP is a water soluble (as opposed to water dispersible) polymer, and was used in these studies in combination with the poorly water soluble drug indomethacin. It is known to be an inhibitor of crystallinity and has been reported to combine with indomethacin at the molecular level [3].

A 1:1 mixture of ethanol and dichloromethane (or 1:1 ethanol/chloroform in the case of the polymer PVP) was found to produce suitable dispersions of relatively low viscosity,

Scanning Electron Microscopy (SEM)

The morphology and size of SEDS particles was investigated using an Hitachi S520 SEM (Hitachi, Japan). Aluminium stubs containing a small quantity of sample particulate were sputter-coated with a gold layer ~300Å thick and viewed and photographed under varying magnifications.

Differential scanning calorimetry (DSC)

This technique was used to measure the crystallinity of samples, given that the lower the order of the crystal lattice the less energy that is required for melting the sample. DSC was used to determine thermal profiles of samples, to monitor the latent heat of fusion (ΔH_f) and to identify any phase or polymorphic transitions and desolvation phenomena, and determine the melting point as well as any glass transition temperatures.

A Perkin-Elmer DSC7 (Perkin-Elmer, USA) was used to determine the crystallinity of the products. Samples (1-3mg) were placed in the sample cell and examined in pierced, crimped aluminium pans, under an atmosphere of nitrogen. The analytical temperature range depended on the drug investigated. Theophylline sublimed just above the melting point, causing difficulties in measuring endotherm peak size. This problem was overcome by adopting a sealed pan method.

X-Ray Powder Diffraction (XRPD)

X-ray powder diffraction was also used as a qualitative technique in support of DSC measurements in assessing the crystallinity of starting materials and prepared samples. Samples were analysed on a D500 XRPD (Siemens, Germany) between 5 and 30 2θ.

UV Spectrophotometry

The weight fraction of drug in the products was measured by UV spectrophotometry assay with an Ultrospec 4000 spectrophotometer (Pharmacia Biotech, Cambridge, England). The absorbance of each polymer was found to be negligible at the wavelengths used.

Dissolution

Dissolution testing was carried out using a stirred-vessel technique with the medium circulated through a flow-cell system and analysed by UV detector.. The dissolution apparatus consisted of a 1litre round-bottomed vessel maintained at around 37°C in a water bath, stirred by paddle at 60rpm. The medium was circulated by means of a peristaltic pump through a 10mm flow-cell. UV readings were taken every 30 seconds using an Ultrospec 4000 spectrophotometer (Pharmacia Biotech, Cambridge, England) and analysed for up to between 30 and 60 minutes.

Three of the model systems were analysed:- paracetamol/HPMC, theophylline/EC and indomethacin/HPMC The specific conditions for the individual systems were:-

Results

The analytical results of the various experimental runs (in particular yield, morphology and drug loading) are summarised in Tables 2 (ascorbic acid), 3 (carbamazepine), 4 & 5 (indomethacin), 6 & 7 (ketoprofen), 8 (paracetamol) and 9 (theophylline), below. These tables also indicate the operating conditions (temperature and pressure within the particle formation vessel, fluid flow rates, solution concentrations and nozzle tip (outlet) diameter) used for each run.

The products of the experiments were in the form of finely dispersed particulates; all were non-cohesive, easy-flowing powders with good handling properties. Their morphology was assessed using SEM, which revealed the non-crystalline products typically as fine web-like structures consisting of agglomerated, roughly spherical particles of the order of 0.05-1 micron diameter. The homogeneity in the appearance of the particles suggested they comprised molecular-level dispersions. Above the amorphous limits detected, mixtures of such web structures with additional, larger drug crystals were observed in many cases.

Figures 2-13 are SEM photographs of some of the starting materials and products of the experiments. Specifically, Figures 2-7 show indomethacin and Figures 8-13 paracetamol.

Figures 14-16 show dissolution profiles for three of the systems investigated, namely paracetamol:HPMC (Figure 14), theophylline:EC (Figure 15) and indomethacin:HPMC (Figure 16). The labelling corresponds to that used in Tables 2-9 for the various experimental runs; X (%) is the maximum concentration of the amorphous phase of the drug prior to the detection of crystallinity.

In all three systems whose dissolution profiles were examined, there were significant differences in drug release rates between the experimental products and purely physical mixes of the relevant drug and polymer, suggesting that the products of the present invention had been formed as intimate molecular level dispersions of a drug in a polymer matrix. For instance, the release of theophylline was significantly inhibited by coformulating it with EC, that of paracetamol was also slightly inhibited by coformulation with HPMC, whilst the dissolution rate of indomethacin was increased on coformulation with HPMC (including one sample above the amorphous detected limit).

Experiment	Drug Conc. (%w/v)	Polymer	Polymer Conc. (%w/v)	Solvent	Solution Flow Rate (ml/min)	Pressure (bar)	CO2 flow (ml/min)	Temp. °C	Nozzle tip diameter (µm)	Yield (%)	Product Description	Size (µm, by SEM)	Morphology (by SEM)	DSC Peaks (ΔH-J/g)	% Drug in Product by UV (Wt%)
LSDA6	2.0	N/A	0	Ethanol	0.2	80	20	50	100	61	Fine white powder	ND	Acicular with some agglomerates	101	NA
LSDA7	0.5	HPMC	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	100	38	Fine white powder	ND	Acicular with some agglomerates	19	41
LSDA8	0.5	HPMC	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	58	Fine white powder	ND	Acicular	47	59
LSDA9	0.25	HPMC	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	48	Fine white powder	ND	Acicular with some agglomerates	22	42
LSDA10	1.0	HPMC	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	85	Fine white powder	ND	Acicular	79	64
LSDA11	0.167	HPMC	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	45	Fine white powder	0.5 x 0.5	Aggregates with some acicular	None	25
LSDA12	1.5	HPMC	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	95	Fine white powder	ND	Acicular	87	87
LSDA13	0.5	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	89	Fine white powder	ND	Acicular	26	43
LSDA14	0.25	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	80	Fine white powder	ND	Acicular	18	29
LSDA15	1.0	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	94	Fine white powder	ND	Acicular	53	60
LSDA16	0.167	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	70	Fine white powder	ND	Acicular	None	24
LSDA17	1.5	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	89	Fine white powder	ND	Acicular with some agglomerates	58	69
LSDA38	0.125	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	85	Fine white powder	ND	ND	None	24
LSDA40	1.167	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	94	Fine white powder	ND	ND	68	70
LSDA42	0.215	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	49	Fine white powder	ND	ND	13	30
LSDA54	0.215	HPMC	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	200	82	Fine white powder	ND	ND	None	28

A two-component nozzle was used in all experiments

NA - Not applicable, ND - Not determined

Experiment	Drug Solvent	Drug Conc. (%w/v)	Polymer	Polymer Conc. (%w/v)	Polymer Solvent	Solution Flow Rate (ml/min)	CO2 flow (ml/min)	Temp (°C)	Pressure (bar)	Nozzle tip diameter (µm)	Yield (%)	Product Description	Size (µm, by SEM)	Morphology (by SEM)	DSC Peaks (ΔH-J/g)	% Drug in Product by UV (Wt %)
RASE58	Ethanol	0.5	EC (7cps)	0.5	Ethanol	0.1	20	37	80	100	12	Fine yellow particulate	100 x150	Amorphous pitted chunks	None	34
RASE59	Ethanol	0.5	EC (7cps)	0.5	Ethanol	0.05	20	37	80	100	19	Fine yellow particulate	100 x150	Amorphous pitted chunks	None	46
RASE60	Ethanol	0.25	EC (7cps)	0.25	Ethanol	0.1	20	37	80	100	19	Fine yellow particulate	100 X 50	Amorphous pitted chunks	None	41
RASE62	(1:1) Ethanol / Chloroform	0.25	PVP (10k)	0.25	(1:1) Ethanol / Chloroform	0.2	20	37	80	100	25	Fine yellow particulate with yellow flakes	100 x150	Amorphous pitted chunks	None	48
RASE63	(1:1) Ethanol / Chloroform	0.75	PVP (10k)	0.25	(1:1) Ethanol / Chloroform	0.2	20	37	80	100	16	Fine yellow particulate with yellow flakes	100 X 50	Amorphous pitted chunks	None	62
RASE64	(1:1) Ethanol / Chloroform	0.75	PVP (10k)	0.25	(1:1) Ethanol / Chloroform	0.2	20	50	80	100	38	Fine yellow particulate	50 x 50, 10 x 0.5, 10 x 5 & 5 x 5	Amorphous pitted chunks with needles, tablets & microspheres	25.3	78
RASE66	(1:1) Ethanol / Chloroform	0.5	PVP (10k)	0.5	(1:1) Ethanol / Chloroform	0.2	20	50	80	100	26	Fine yellow particulate with yellow flakes	250 X 200	Amorphous pitted chunks	None	51
RASE68	(1:1) Ethanol / Chloroform	0.1	PVP (10k)	0.5	(1:1) Ethanol / Chloroform	0.2	20	37	80	100	13	Fine yellow particulate	100 x 100	Amorphous pitted chunks	NA	17
RASE69	(1:1) Ethanol / Chloroform	0.1	PVP (10k)	0.5	(1:1) Ethanol / Chloroform	0.2	20	50	80	100	10	Fine yellow particulate	100 x100	Amorphous pitted chunks	None	20
RASE70	(1:1) Ethanol / Chloroform	0.1	PVP (10k)	0.5	(1:1) Ethanol / Chloroform	0.2	20	37	80	100	8	Fine yellow particulate with yellow flakes	200 x150	Amorphous pitted chunks	None	16
RASE71	(1:1) Ethanol / Chloroform	1.8	PVP (10k)	0.2	(1:1) Ethanol / Chloroform	0.2	20	50	80	100	73	Fine pale yellow particulate	50 x 50, 10 x 0.5, 3 x 2, 1 x 1	Amorphous pitted chunks with needles, tablets & microspheres	62.5	86
RASE72	(1:1) Ethanol / Chloroform	1.8	PVP (10k)	0.2	(1:1) Ethanol / Chloroform	0.2	20	37	80	100	64	Fine pale yellow particulate	50 x 50, 10 x 0.5, 6 x 2, 2 x 2	Amorphous pitted chunks with needles, tablets & microspheres	62.3	81
RASE73	(1:1) Ethanol / Chloroform	0.75	PVP (10k)	0.25	(1:1) Ethanol / Chloroform	0.2	20	50	80	100	43	Fine pale yellow particulate	30 x 30, 5 x 0.2, 2 x 1, 0.5 x 0.5	Amorphous pitted chunks with needles, tablets & microspheres	23.3	67
RASE74	(1:1) Ethanol / Chloroform	0.75	PVP (10k)	0.25	(1:1) Ethanol / Chloroform	0.2	20	37	80	100	13	Fine yellowish white particulate	50 x 50, 5 x 0.2, 5 x 3, 10 x 10	Amorphous pitted chunks with needles, tablets & microspheres	57.2	76
RASE75	(1:1) Ethanol / Chloroform	0.75	PVP (10k)	0.25	(1:1) Ethanol / Chloroform	0.2	20	60	80	100	83	Fine yellow particulate	20 x 5, 5 x 0.5, 4 x 2, 1 x 1	Amorphous chunks with needles, tablets & microspheres	29.1	76
LSDA57	(1:1) Ethanol / Chloroform	0.168	EC 7cps	0.5	1:1 Ethanol:DCM	0.2	20	37	80	100	30	Yellow powder	ND	ND	None	10
LSDA58	(1:1) Ethanol / Chloroform	0.170	EC 7cps	0.5	1:1 Ethanol:DCM	0.2	20	50	80	100	11	Yellow powder	ND	ND	None	22
LSDA59	(1:1) Ethanol / Chloroform	0.5	EC 7cps	0.5	1:1 Ethanol:DCM	0.3	20	34	80	100	17	Yellow powder	ND	ND	None	20
LSDA60	Ethanol	1.517	EC 7cps	0.5	Ethanol	0.2	20	34	100	100	ND	Yellow powder	ND	ND	None	34
LSDA61	Ethanol	0.339	EC 7cps	0.5	Ethanol	0.2	12	34	80	100	10	Yellow powder	ND	ND	None	13
LSDA63	Ethanol	1.515	EC 7cps	0.5	Ethanol	0.1	15	50	80	100	89	Fine white powder	ND	ND	68	85
LSDA64	Ethanol	0.5	EC 7cps	0.5	Ethanol	0.1	15	50	80	100	67	Fine off-white powder	ND	ND	37	50
LSDA65	Ethanol	1.0	EC 7cps	0.5	Ethanol	0.1	15	50	80	100	89	Fine off-white powder	ND	ND	51	70
LSDA66	Ethanol	0.341	EC 7cps	0.5	Ethanol	0.1	15	50	80	100	4	Fine white powder	ND	ND	31	42

A two-component nozzle was used in all experiments

NA - Not applicable, ND - Not determined

[redacted]

Experiment	Drug Conc. (%w/v)	Polymer	Polymer Conc'n (%w/v)	Solvent	Solution Flow Rate (ml/min)	CO2 flow (ml/min)	Temp (°C)	Pressure (bar)	Nozzle tip diameter (µm)	Yield (%)	Product Description	Size (µm, by SEM)	Morphology (by SEM)	DSC Peaks (ΔH - J/g)	% Drug in Product by UV (Wt %)
RASG14	0.5	EC 7cps	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	0	No product	NA	NA	NA	NA
RASG15	0.5	EC 7cps	0.5	Ethanol / DCM (1:1)	0.1	20	37	80	200	10	White cobs	ND	ND	ND	NA
LSDA22	0.5	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	100	31	Fine white powder	NA	Aggregates	None	22
LSDA23	0.167	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	45	Fine white powder	NA	Aggregates	None	7
LSDA24	0.25	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	39	Fine white powder	NA	Aggregates	None	11
LSDA25	1.0	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	7	Fine white powder	NA	Aggregates	None	25
LSDA26	1.5	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	0	ND	ND	Aggregates	1	ND
LSDA27	4.5	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	0	No product	NA	NA	NA	NA
LSDA28	4.5	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	0	No product	NA	NA	NA	NA
LSDA29	4.5	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	3	Fine white powder	ND	ND	None	49
LSDA30	4.5	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	2	Fine white powder	ND	ND	None	52
LSDA36	4.5	HPMC	0.5	Ethanol / DCM (1:1)	0.05	10 N	35	80	200	1	Fine white powder	ND	ND	83	84
LSDA39	2.25	HPMC	0.25	Ethanol / DCM (1:1)	0.05	20 N	50	80	200	0	No product	NA	NA	NA	NA

All experiments used a two component nozzle

NA - Not applicable, ND - Not determined

N - In these two experiments, nitrogen was substituted for CO2 (flows are in l/min measured at ambient conditions)

Theophylline Result Table 9

Experiment	Drug Conc'n (%w/v)	Polymer	Polymer Conc. (%w/v)	Solvent	Solution Flow Rate (ml/min)	CO2 Flow Rate (ml/min)	Temp (°C)	Pressure (bar g)	Nozzle tip diameter (µm)	Yield (%)	Product Description	Size (µm, by SEM)	Morphology (by SEM)	DSC Peaks °C (ΔH - J/g)	% Drug in Product by UV (Wt %)
RASH1	0.17	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	20	37	80	200	60	Fine white particulate	<0.1 x 0.1	Amorphous aggregate	None	3
RASH2	0.17	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	73	Fine white particulate	20 x 20 & 0.1 x 0.1	Amorphous aggregate / tabular	None	28
RASH3	0.17	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.2	20	37	80	200	73	Fine white particulate	0.1 x 0.1	Amorphous aggregate	None	5
RASH4	0.5	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	20	37	80	200	78	Fine white particulate, some cobs	<0.1 x 0.1 / 20 x 5 / 30 x 1	Amorphous aggregate / platy / acicular	44.5	38
RASH5	0.5	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	85	Fine white particulate, some cobs	<0.1 x 0.1 / 50 x 30 / 3 x 0.1	Amorphous aggregate / platy / acicular	76.2	46
RASH6	0.5	EC 7cps	0.5	Ethanol	0.2	20	37	80	200	13	Fine white particulate, some cobs	5 x 5	Amorphous aggregate	None	9
RASH7	0.5	EC 7cps	0.5	Ethanol	0.1	20	37	80	200	30	Fine white particulate	5 x 5	Amorphous aggregate	None	5
RASH8	0.33	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	20	37	80	200	69	Fine white particulate, some cobs	0.1 x 0.1 / 20 x 5 / 5 x 0.5	Amorphous aggregate / platy / acicular	14.3	21
RASH9	0.33	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	74	Fine white particulate, some cobs	0.5 x 0.5 / 20 x 10 / 20 x 1	Amorphous aggregate / platy / acicular	41.2	59
RASH10	0.17	EC 7cps	0.5	Ethanol	0.1	20	50	80	200	41	Fine white particulate	2 x 2 / 70 x 50	Amorphous aggregate / platy	None	28
RASH11	0.5	EC 7cps	0.5	Ethanol / DCM (1:1)	0.3	20	34	80	100	47	Fine white particulate	1 X 1 / 2 x 6	Amorphous aggregate / platy	30.3	34
RASH12	0.5	EC 7cps	0.5	Ethanol / DCM (1:1)	0.3	20	50	80	100	78	Fine white particulate	2 x 10	Amorphous aggregate / platy	55.2	48
RASH13	0.17	EC 7cps	0.5	Ethanol / DCM (1:1)	0.3	20	50	80	100	43	Fine white particulate	2 x 2 / 6 x 2	Amorphous aggregate / platy	ND	17
RASH14	0.25	EC 7cps	0.5	Ethanol / DCM (1:1)	0.3	20	50	80	100	49	Fine white particulate	2 x 2 / 8 x 2	Amorphous aggregate / platy	None	27
RASH15	1.0	EC 7cps	0.5	Ethanol / DCM (1:1)	0.3	20	50	80	100	92	Fine white particulate	ND	ND	77.3	67
LSDA41	0.33	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.2	20	37	80	500	44	Fine white powder	ND	ND	None	35
LSDA44	0.056	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	20	50	80	200	6	Fine white powder	ND	ND	None	7
LSDA45	0.056	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.2	20	50	80	200	33	Fine white powder	ND	ND	None	2
LSDA52	0.125	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	20	50	80	200	ND	ND	ND	ND	None	17
LSDA53	0.125	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	20	50	80	200	76	Fine white powder	ND	ND	16.0	20
LSDA55	0.172	EC 7cps	0.5	Ethanol / DCM (1:1)	0.3	20	50	80	100	58	Fine white powder	ND	ND	7.9	26
LSDA56	1.515	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	14	Fine white powder	ND	ND	83.7	71

All experiments used a two component nozzle

NA - Not applicable, ND - Not determined

·5°C, when analysed at a scanning rate of 20°C/min. This peak shifts to lower temperature coformulated indomethacin:PVP systems. Figures 29 and 30 show DSC profiles for, spectively, the crystalline raw material and the indomethacin:PVP system prepared in perimental run RASE 64. The peak at 139°C in Figure 30 indicates the presence of ystalline indomethacin in the sample (which contained 78% w/w indomethacin, with 30% ystallinity).

Other indomethacin:PVP samples were assessed both initially and after 12 months' orage in a dessicator at 2-8°C. The results are tabulated in Table 10 below. The ırresponding DSC scans are shown in Figures 31-40 respectively. In all of those figures, ıere is no peak at 139°C, indicating an absence of crystalline indomethacin in the samples ·sted, both initially and after 12 months' storage.

able 10

Sample Reference	Storage Time	Indomethacin Content (%)	Result
RASE70	Initial	16	No crystallinity
RASE70	12 month	16	No crystallinity
RASE69	Initial	20	No crystallinity
RASE69	12 month	20	No crystallinity
RASE62	Initial	48	No crystallinity
RASE62	12 month	48	No crystallinity
RASE66	Initial	51	No crystallinity
RASE66	12 month	51	No crystallinity
RASE63	Initial	62	No crystallinity
RASE63	12 month	62	No crystallinity

drug:polymer dispersion and intermolecular/interpolymeric chain mixing and interaction would occur at equivalence of total specific (i.e. polar and hydrogen bonding) solubility parameters, δ_s , for drug and polymer. It was further hypothesised that the point of maximum compatibility, i.e. when $\delta_s^d - \delta_s^p = 0$ (where δ_s^d and δ_s^p represent the total specific solubility parameter for the drug and polymer respectively), would correspond to the point when the maximum amount of drug can exist in an amorphous phase. A reduction in this level would occur as $\delta_s^d - \delta_s^p$ attains either a positive or negative value.

Table 11 lists calculated values of $\delta_s^d - \delta_s^p$ together with values of X% (range).

Table 11 Calculated values of $(\delta_{s-}^d \delta_s^p)$ and X (midpoint and range) for drug-polymer systems

Drug/Polymer	$(\delta_{s-}^d \delta_s^p)$	X (%) midpoint	Range
Ascorbic acid/EC	20.7	12.5	10-15
Ascorbic acid/HPMC	16.8	37.5	35-40
Carbamazepine/EC	-0.2	25.0	20-30
Carbamazepine/HPMC	-4.1	32.5	25-40
Paracetamol/EC	4.8	6.0	1-12
Paracetamol/HPMC	0.9	30.0	25-35
Indomethacin/EC	-1.7	23.0	18-28
Indomethacin/HPMC	-5.6	40.0	35-45
Theophylline/EC	5.9	25.0	20-30
Theophylline/HPMC	2.0	12.5	5-20

It seems likely that other factors play critical roles in determining the final phase mposition and structure of drug:polymer coformulations prepared using SEDS. Such tors could for instance include solute-solvent interactions taking place during the rapid rticle formation process. In the present study, solvents and co-solvents were selected to ɔvide at least some solubility for all drugs and polymers examined. The different affinity for various solutes and level of solute saturation in the solvent system, during the extremely ort (microseconds) solvent extraction period and the intensive mixing events occurring, will y critical roles in these events. The data indicate that these effects are more pronounced for drug:HPMC systems than for the drug:EC systems. In the former, a stronger solvation ect and interaction with components may lead to increased amorphous drug content in the oduct at positive and negative values of $\delta_s^d - \delta_s^p$.

It is interesting to note the different characteristics and behaviour of the two racetamol:polymer systems. It is known that previous attempts to form amorphous racetamol, using conventional particle formation techniques, have on the whole proved successful, this being attributed to the high crystallinity and crystal energy of paracetamol. owever, by using SEDS to coformulate paracetamol with for instance HPMC, a particulate oduct containing between 25 and 35% of the amorphous drug can be prepared.

The indomethacin:PVP system highlights yet further the potential benefits of ocessing using SEDS, again because of the high levels of amorphous drug achievable which turn can reduce the amount of polymer required in drug delivery systems. Indomethacin is ɔorly soluble in aqueous media and PVP is widely used in industry to enhance the solubility f such drugs. Using SEDS, a particulate product containing over 60% amorphous domethacin, with good stability, has been formed. This suggests a greatly increased level of teraction between the drug and PVP, compared to that between the drug and either EC or PMC.

The structure of the stable γ-indomethacin polymorph is shown in Figure 43. The rrangement is stabilised by hydrogen bonding between carboxyl groups forming a cyclic imer.

The reason for the relatively high level of incorporation of indomethacin in PVP is elieved to result from hydrogen bonding between the oxygen on the pyrrolidone ring of PVP nd the hydrogen on the carboxyl group of indomethacin [9]. This disrupts the intermolecular ydrogen bonding of the γ-indomethacin polymorph, interfering with the long-range crystalline rder and linking the indomethacin molecules instead to the polymer backbone, as shown in igure 44.

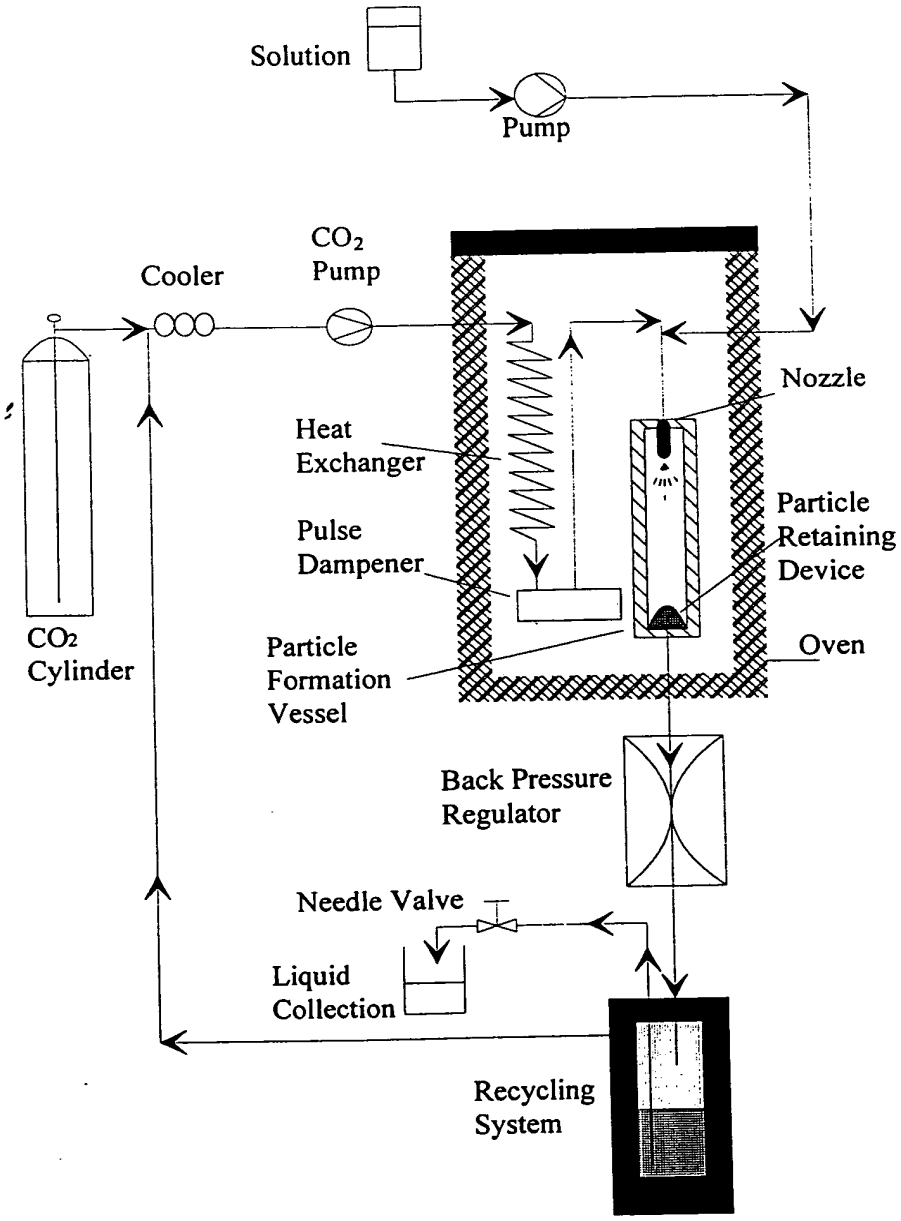
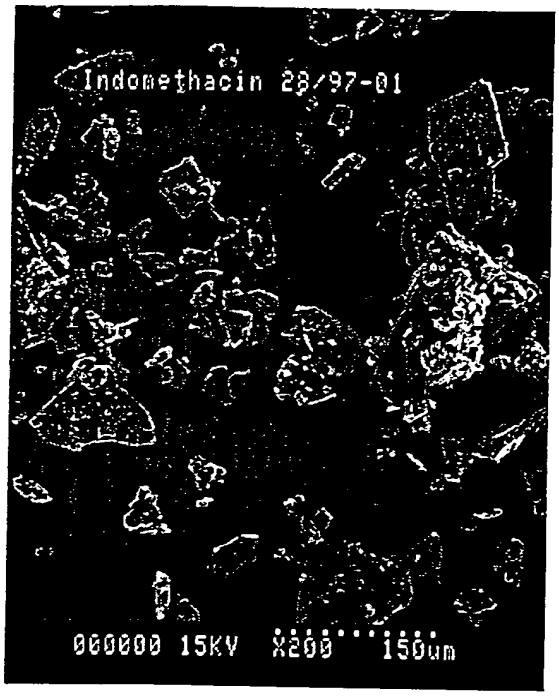
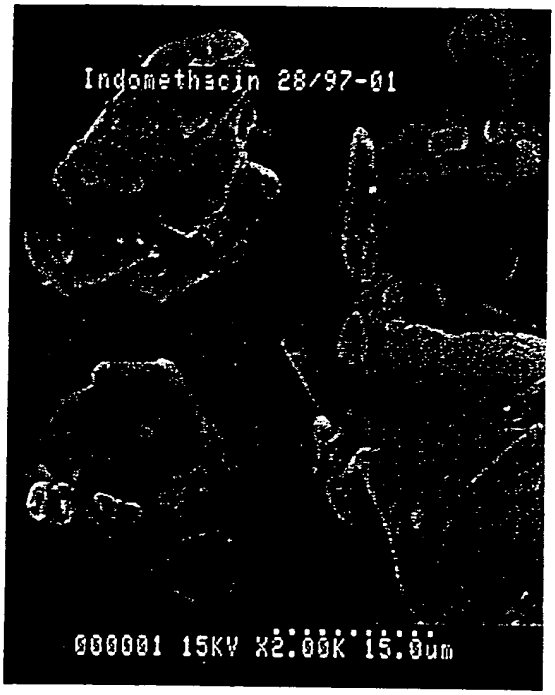

Solution
Pump
CO_2 Pump
Cooler
Nozzle
Heat Exchanger
Particle Retaining Device
Pulse Dampener
CO_2 Cylinder
Particle Formation Vessel
Oven
Back Pressure Regulator
Needle Valve
Liquid Collection
Recycling System

FIGURE 1



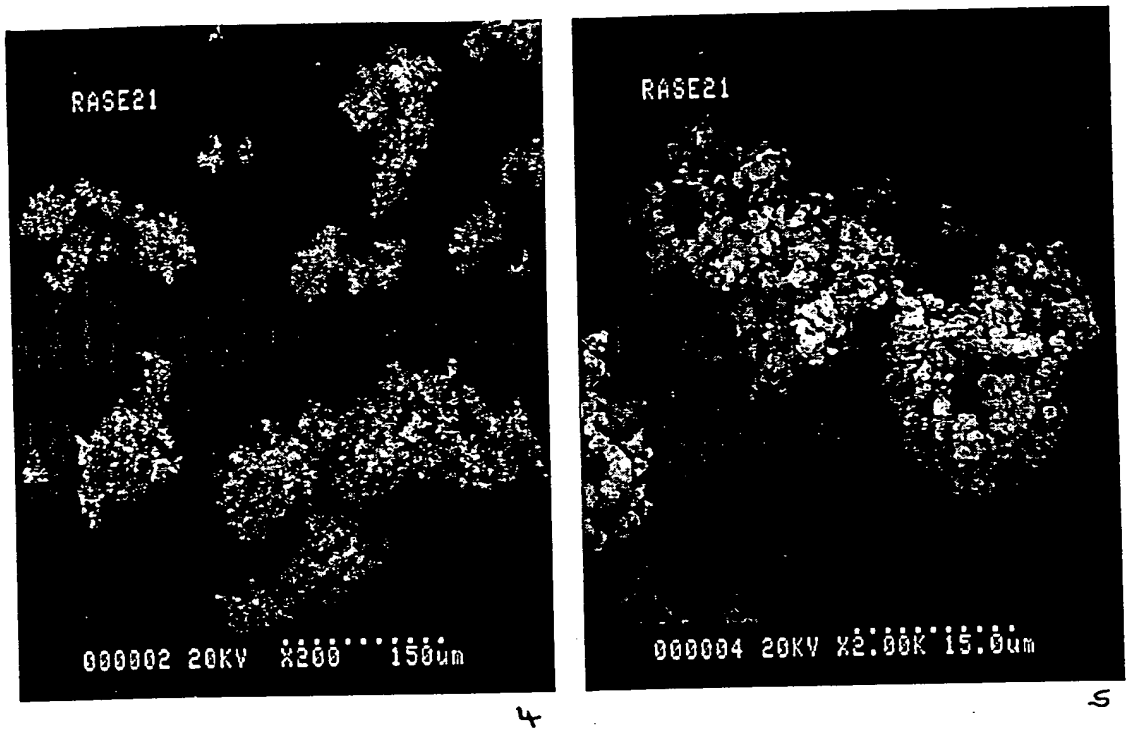
2



3

Figures 2&3 Indomethacin raw material (28/97-01 lot1)

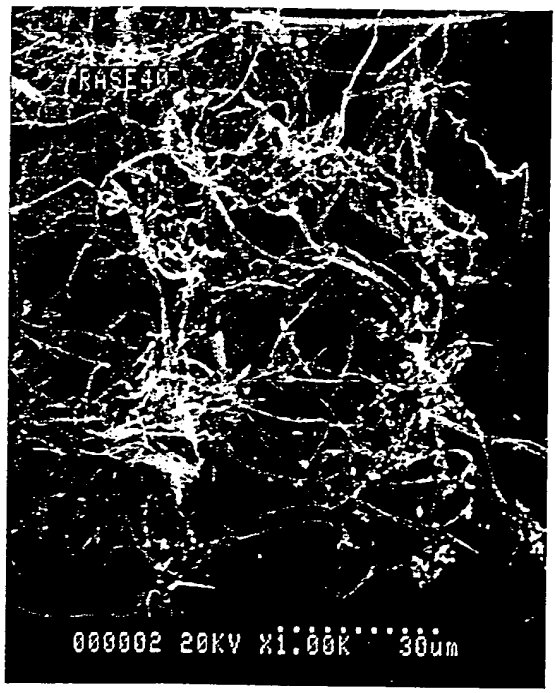
(200 and 2000 x magnification)



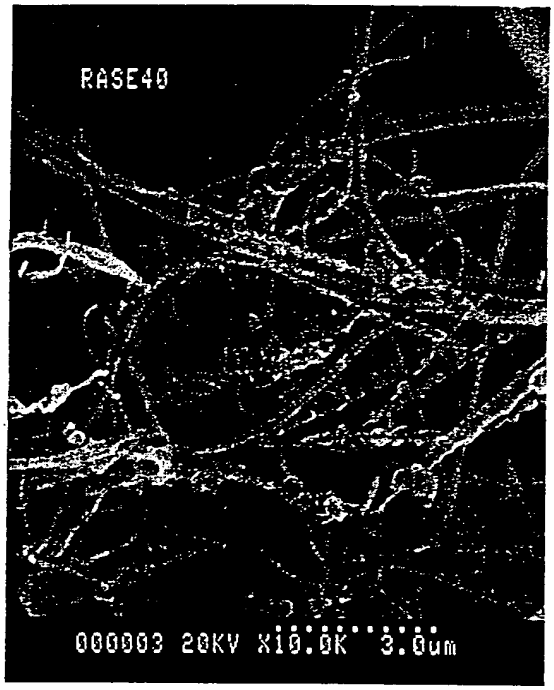
4 5

Figures 4 & 5 Amorphous indomethacin/HPMC (RASE21)

(200 and 2000 x magnification)



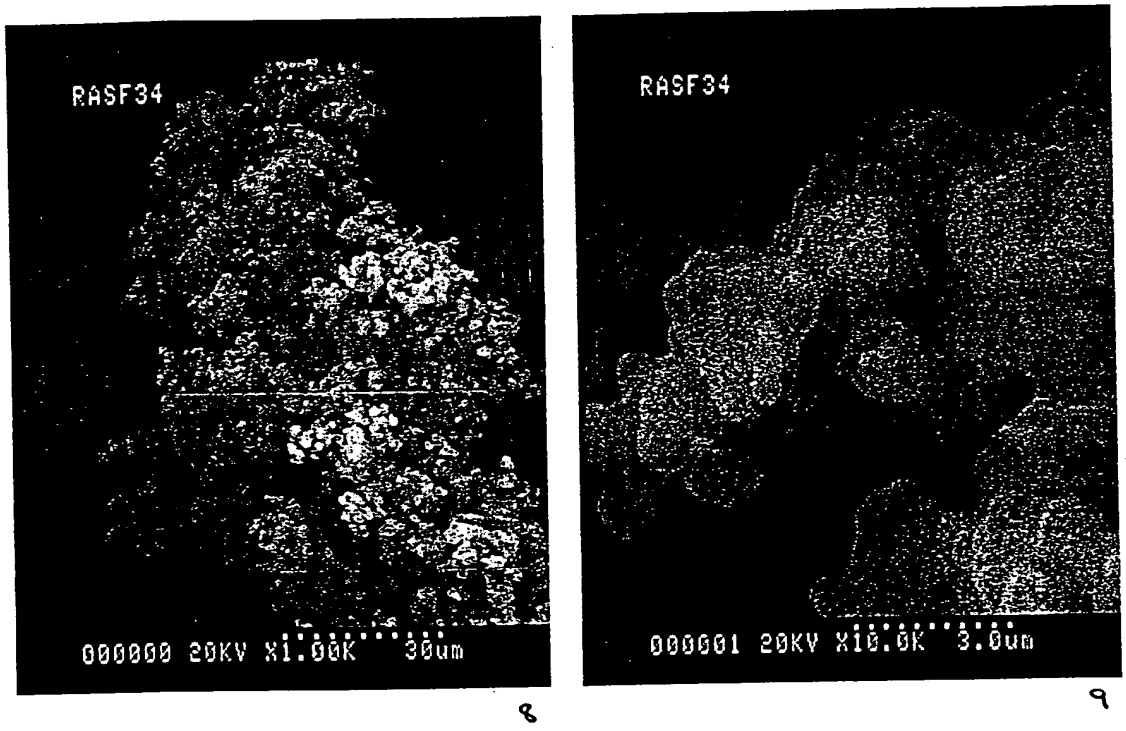
6



7

Figures 6 & 7 Partially crystalline indomethacin/HPMC (RASE40)

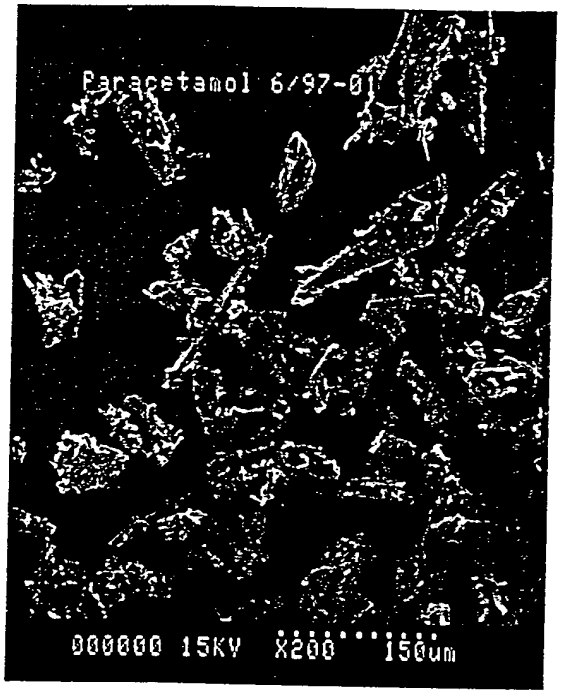
(1000 and 10,000 x magnification)



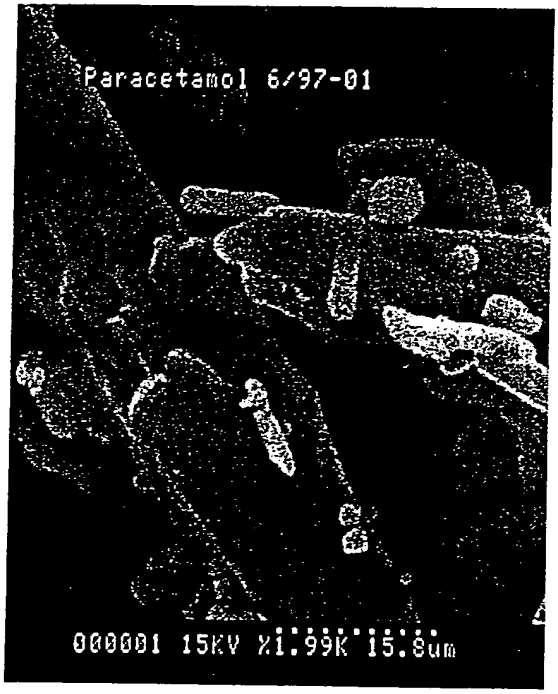
๘ ๙

Figures ๘&๙ Amorphous Paracetamol/HPMC (RASF34)

(1000 and 10,000 x magnification)



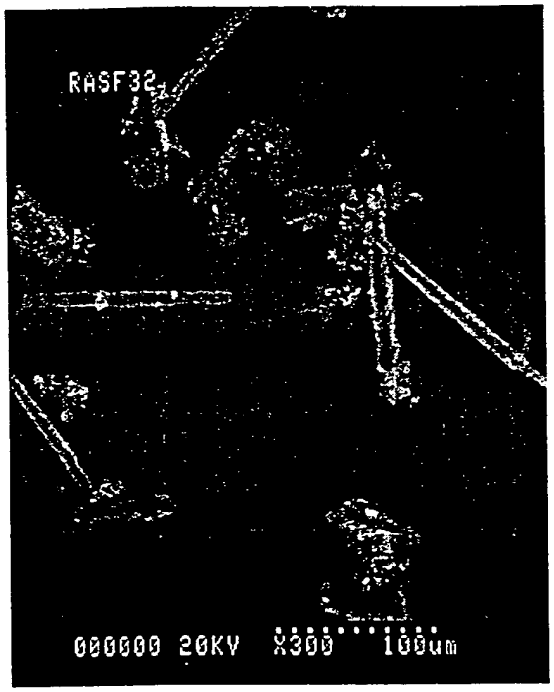
10



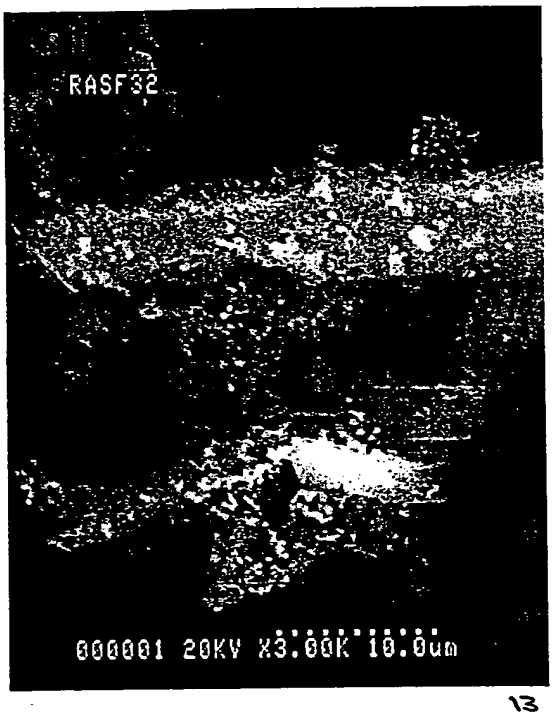
11

Figures 10 & 11 Paracetamol raw material (06/97-01 lot3)

(200 and 1990 x magnification)



12



13

Figures 12 & 13 **Partially crystalline paracetamol/HPMC (RASF32)**

(100 and 1000 x magnification)

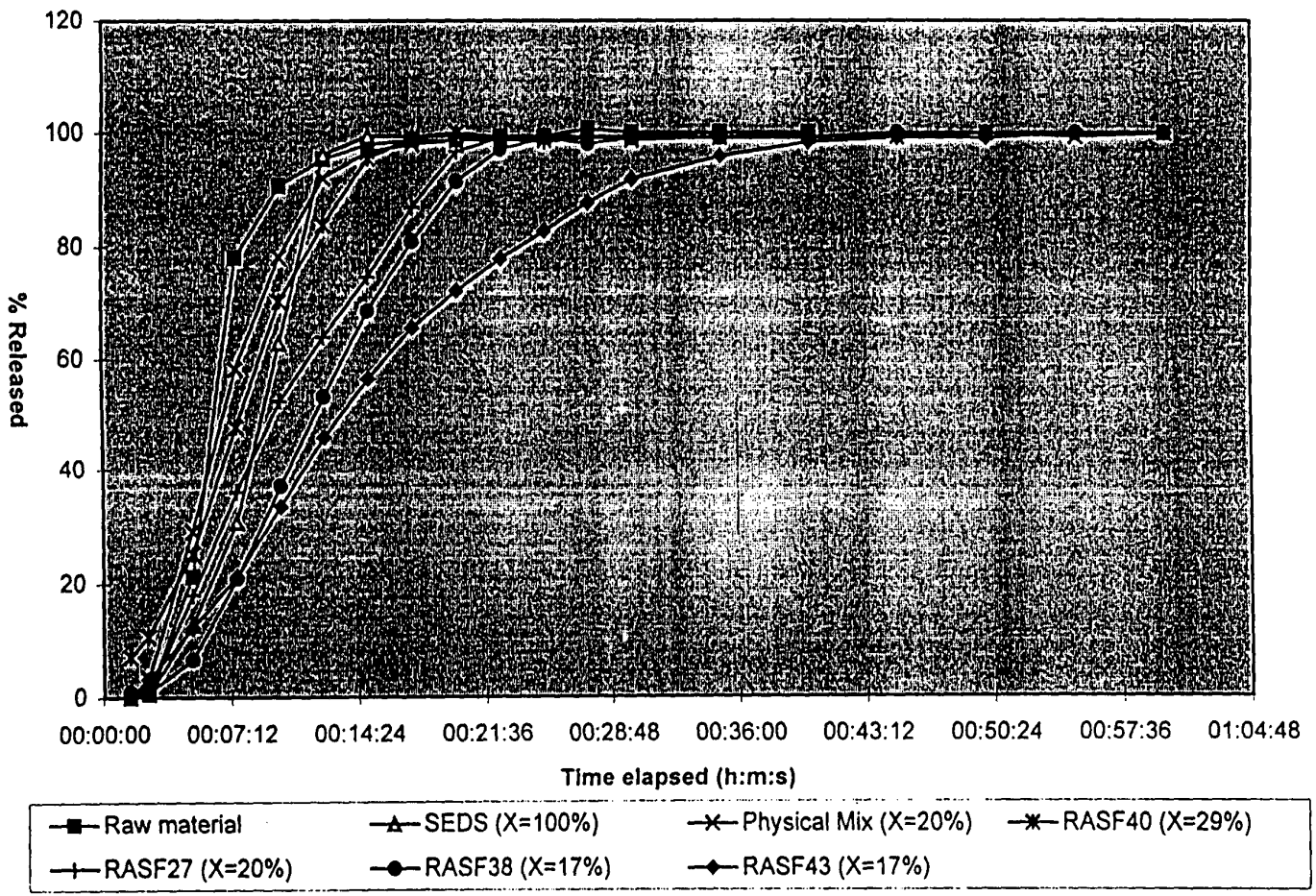

Dissolution Profiles :- Paracetamol/HPMC
120
100
80
60
40
20
0
% Released
00:00:00
00:07:12
00:14:24
00:21:36
00:28:48
00:36:00
00:43:12
00:50:24
00:57:36
01:04:48
Time elapsed (h:m:s)
Raw material
SEDS (X=100%)
Physical Mix (X=20%)
RASF40 (X=29%)
RASF27 (X=20%)
RASF38 (X=17%)
RASF43 (X=17%)

FIGURE 14

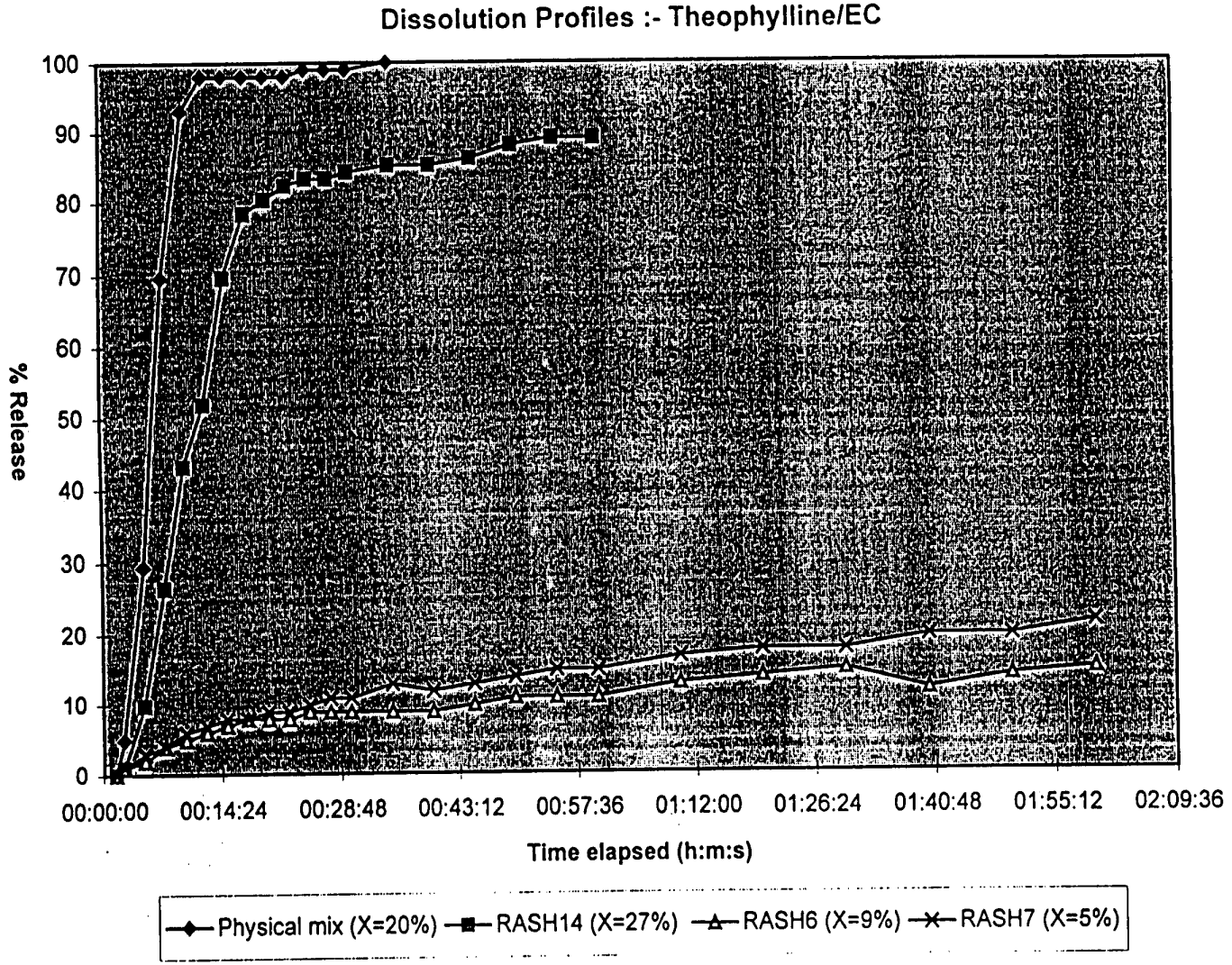

Dissolution Profiles :- Theophylline/EC
100
90
80
70
60
50
40
30
20
10
0
% Release
00:00:00
00:14:24
00:28:48
00:43:12
00:57:36
01:12:00
01:26:24
01:40:48
01:55:12
02:09:36
Time elapsed (h:m:s)
Physical mix (X=20%)
RASH14 (X=27%)
RASH6 (X=9%)
RASH7 (X=5%)

FIGURE 15

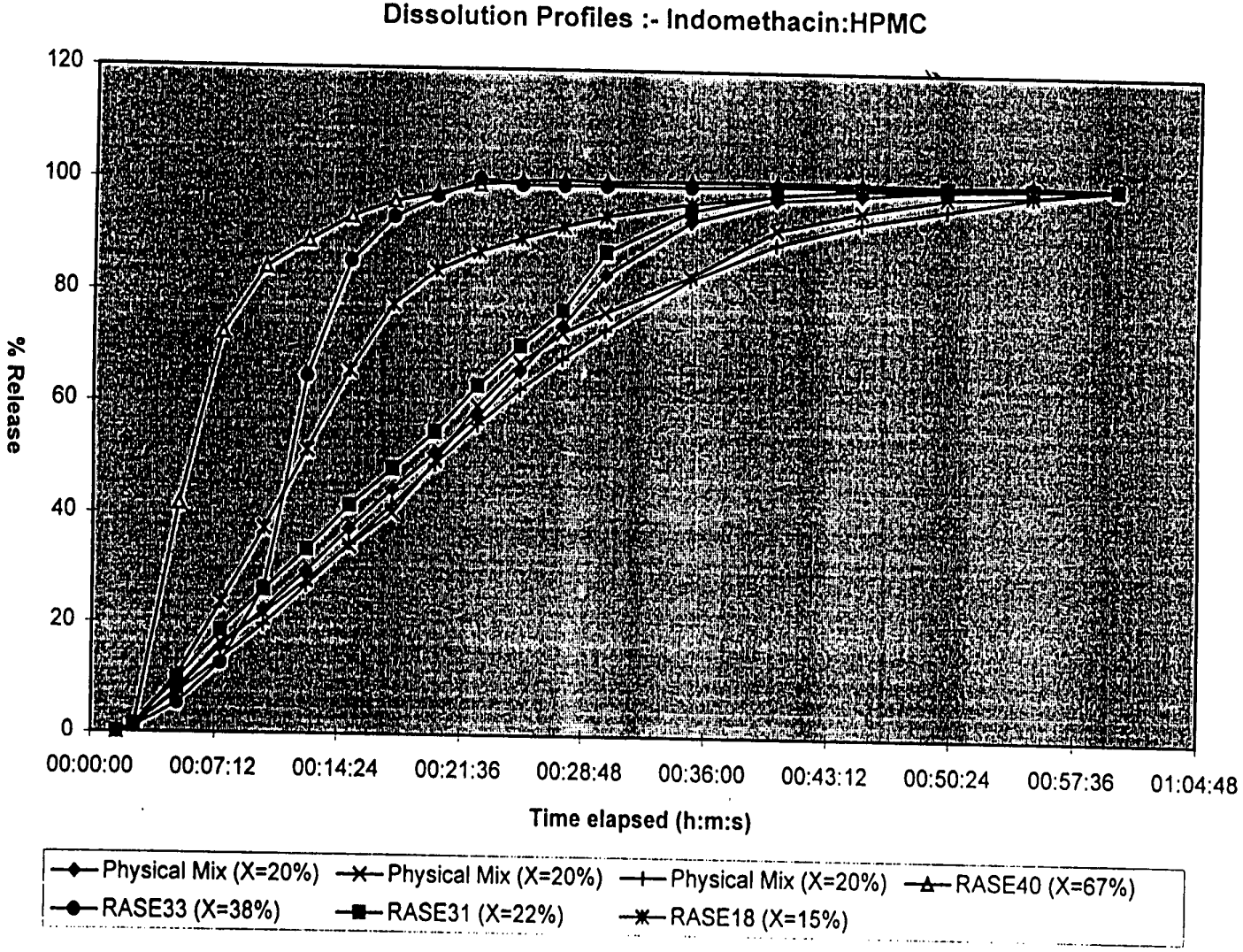

Dissolution Profiles :- Indomethacin:HPMC
120
100
80
60
40
20
0
% Release
00:00:00
00:07:12
00:14:24
00:21:36
00:28:48
00:36:00
00:43:12
00:50:24
00:57:36
01:04:48
Time elapsed (h:m:s)
Physical Mix (X=20%)
Physical Mix (X=20%)
Physical Mix (X=20%)
RASE40 (X=67%)
RASE33 (X=38%)
RASE31 (X=22%)
RASE18 (X=15%)

FIGURE 16

Figure 17 Ascorbic acid:EC

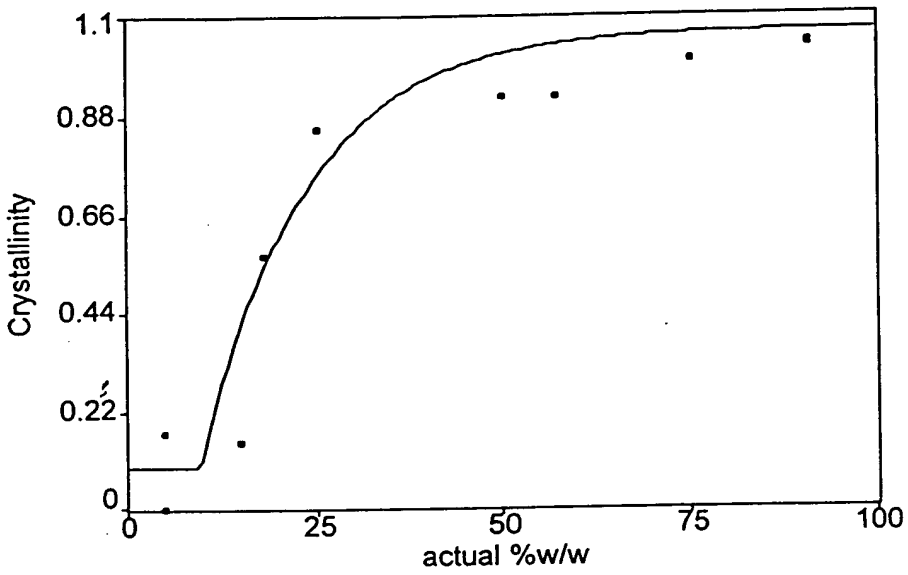


Figure 18 Ascorbic Acid:HPMC

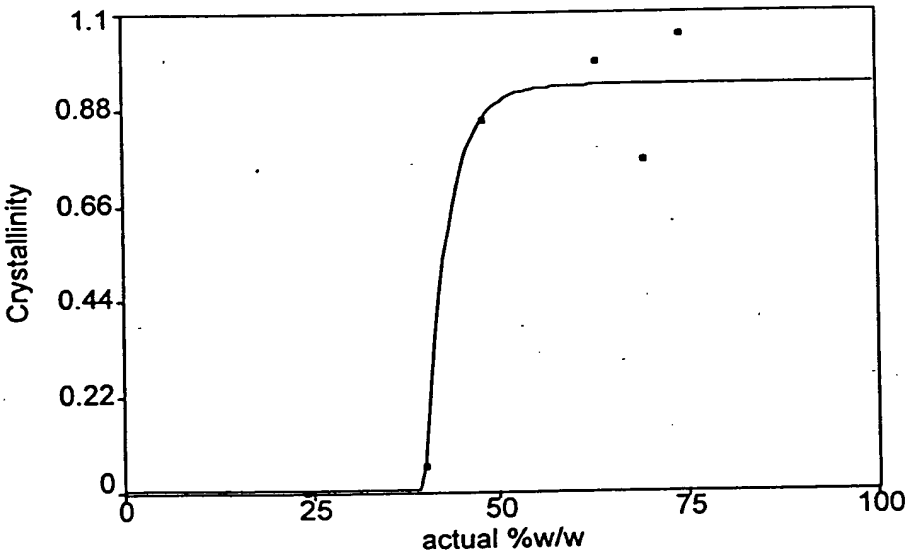


Figure 19 Carbamazepine:EC

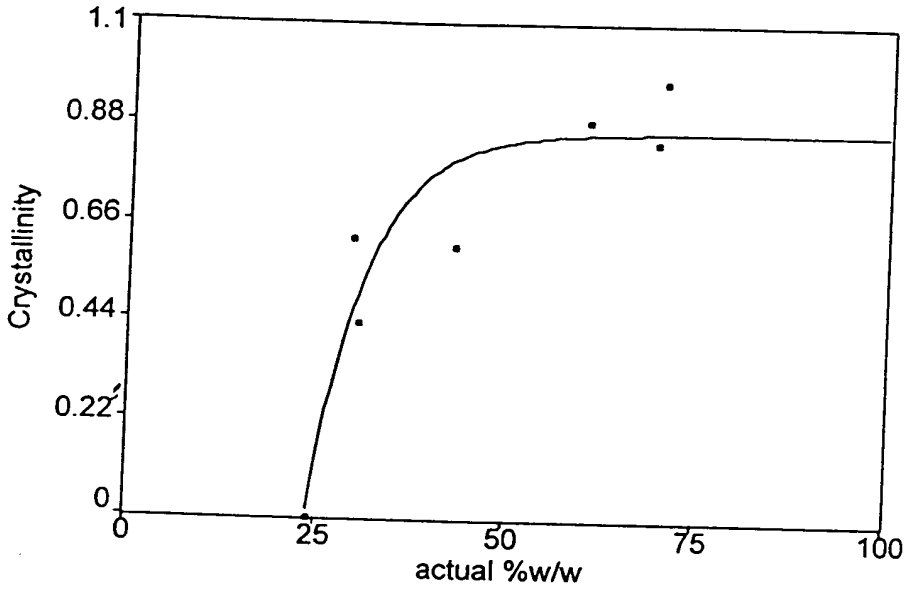


Figure 20 Carbamazepine:HPMC

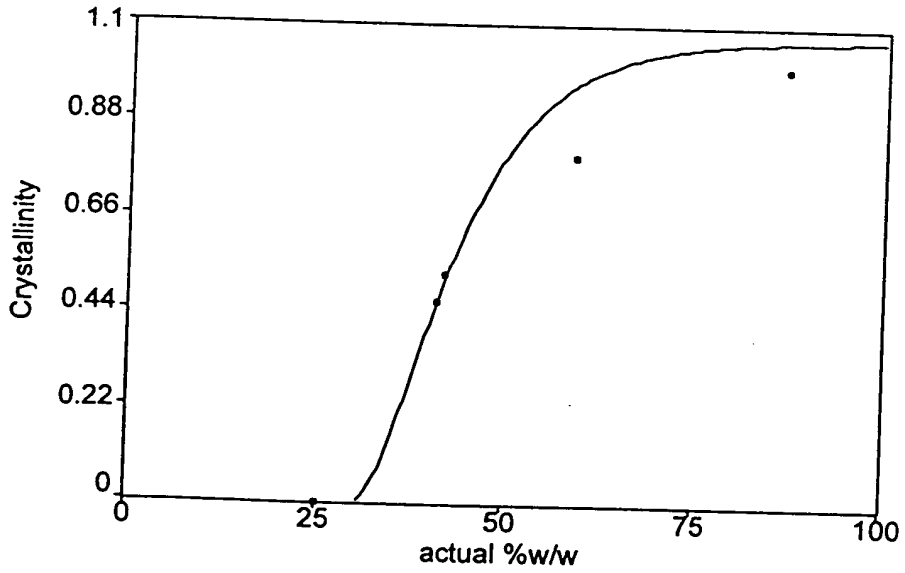


Figure ๒๑ · **Indomethacin:EC**

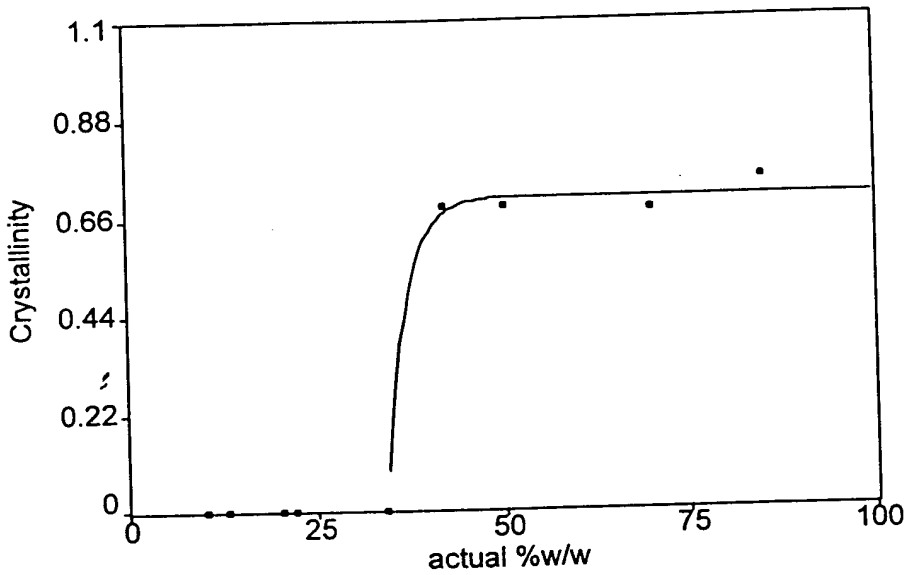


Figure ๒๒ **Indomethacin:HPMC**

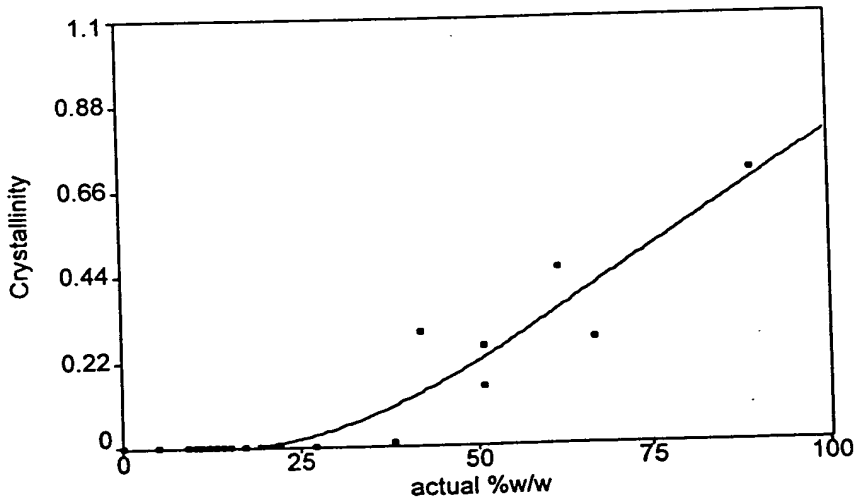


Figure 23 **Indomethacin:PVP**

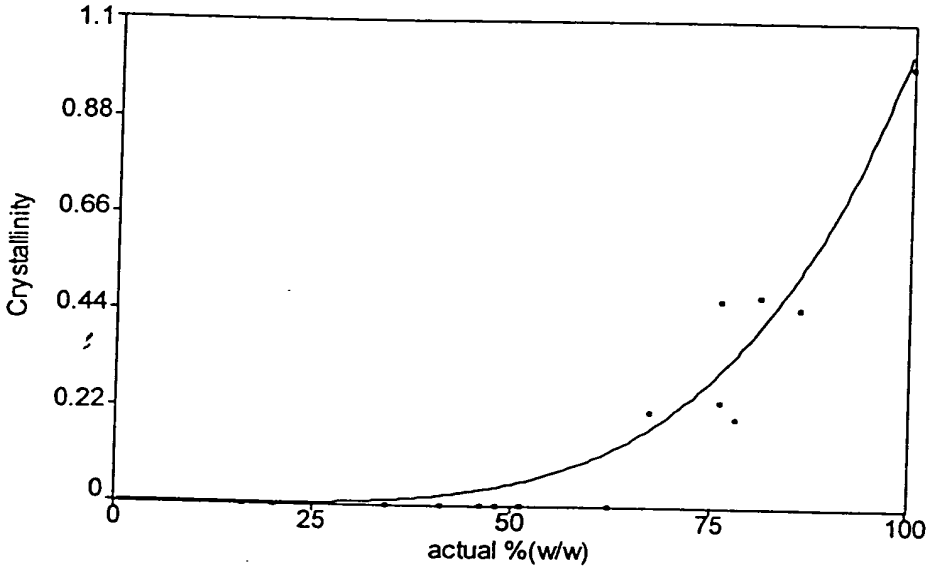


Figure ๒๔ Paracetamol:EC

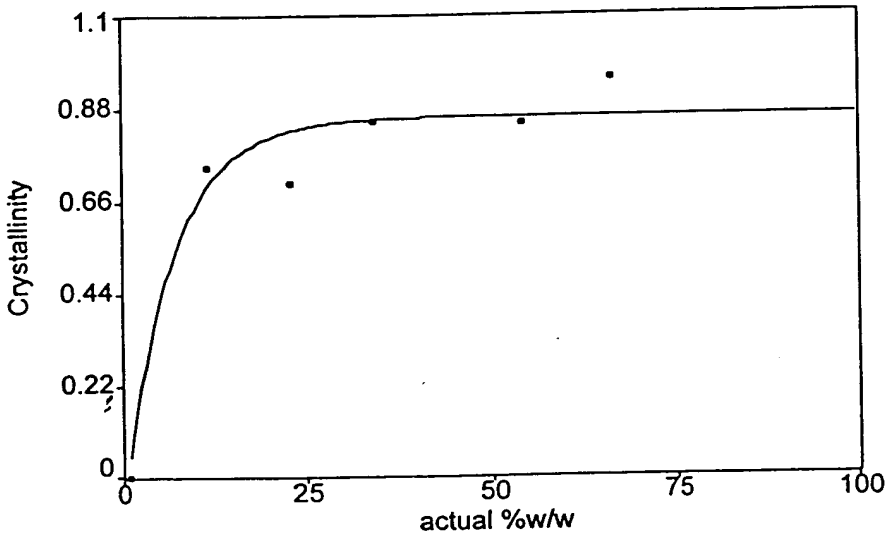


Figure ๒๕ Paracetamol:HPMC

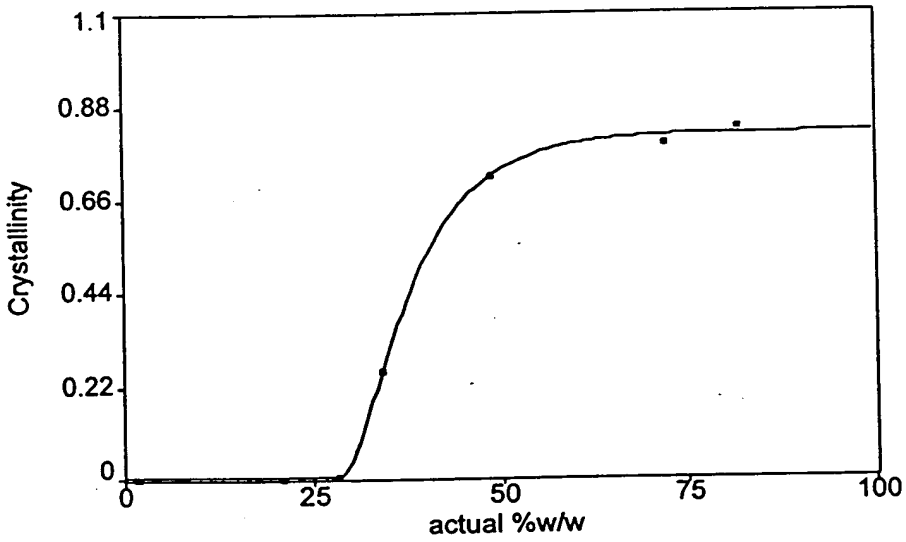


Figure २६ Theophylline:EC

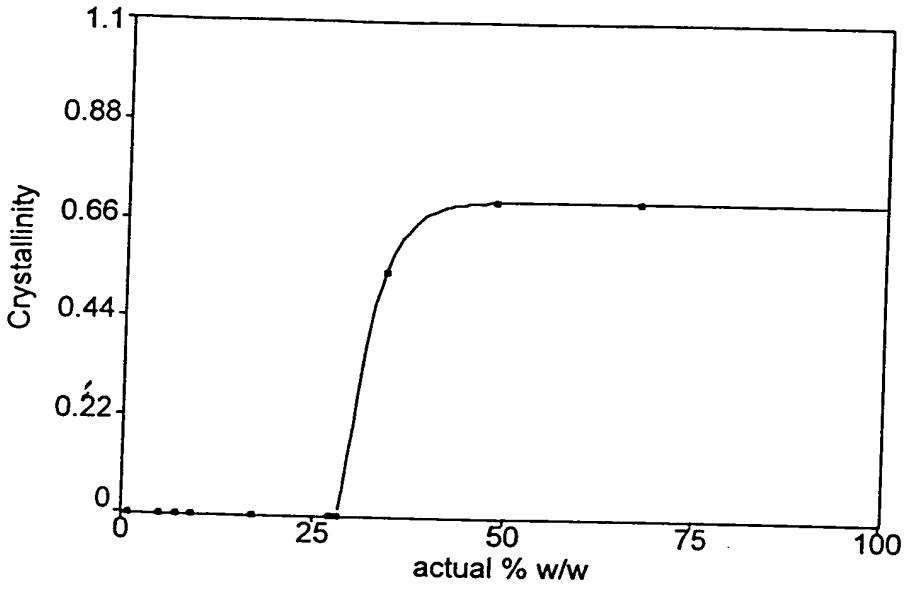


Figure २७ Theophylline:HPMC

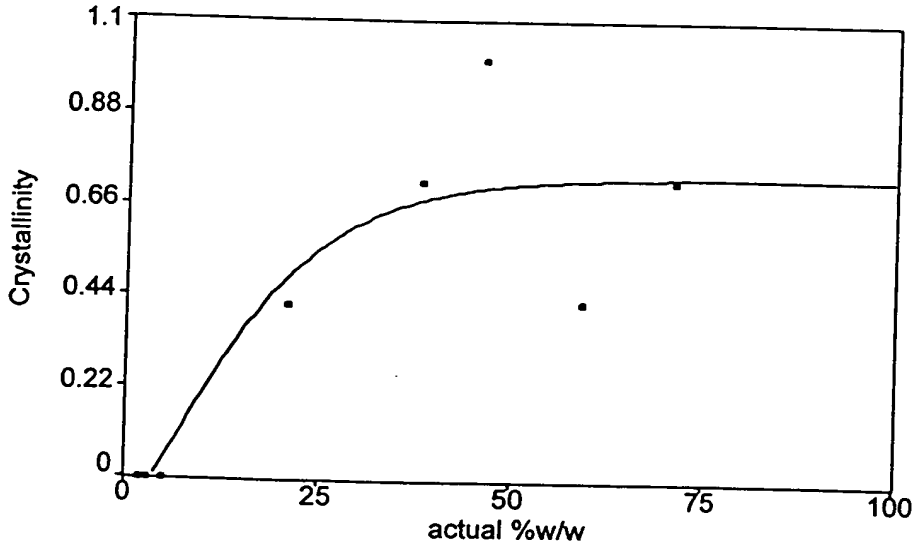
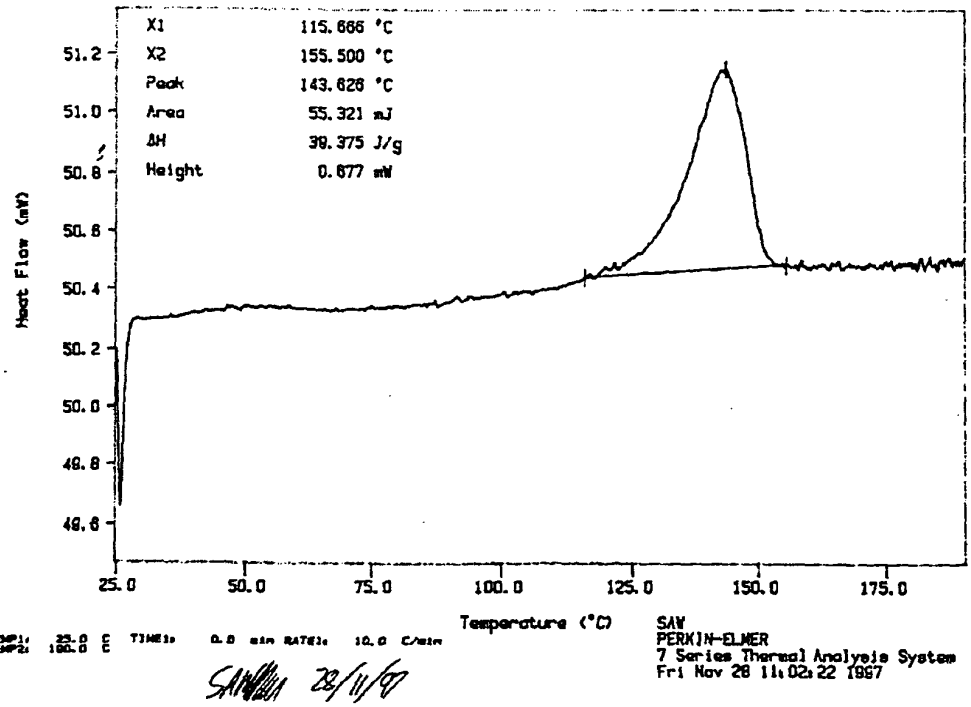


Figure 28 Example of a Differential Scanning Calorimetry (DSC) Trace

Curve 1: DSC
File info: SWRASE27 Fri Nov 28 10:58:40 1997
Sample Weight: 1.405 mg
RASE27



28/11/97

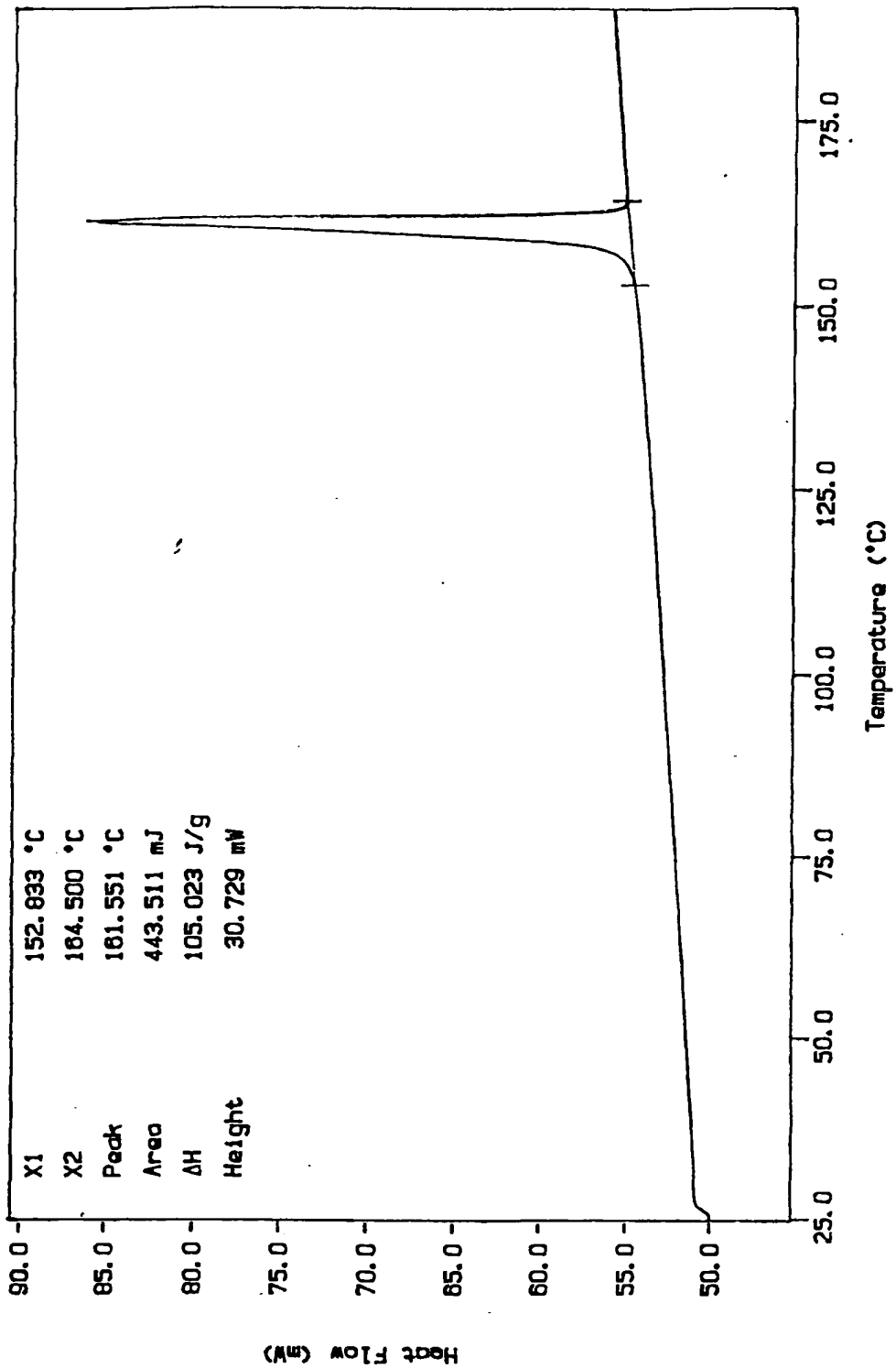


Figure 29 Indomethacin raw material DSC scan

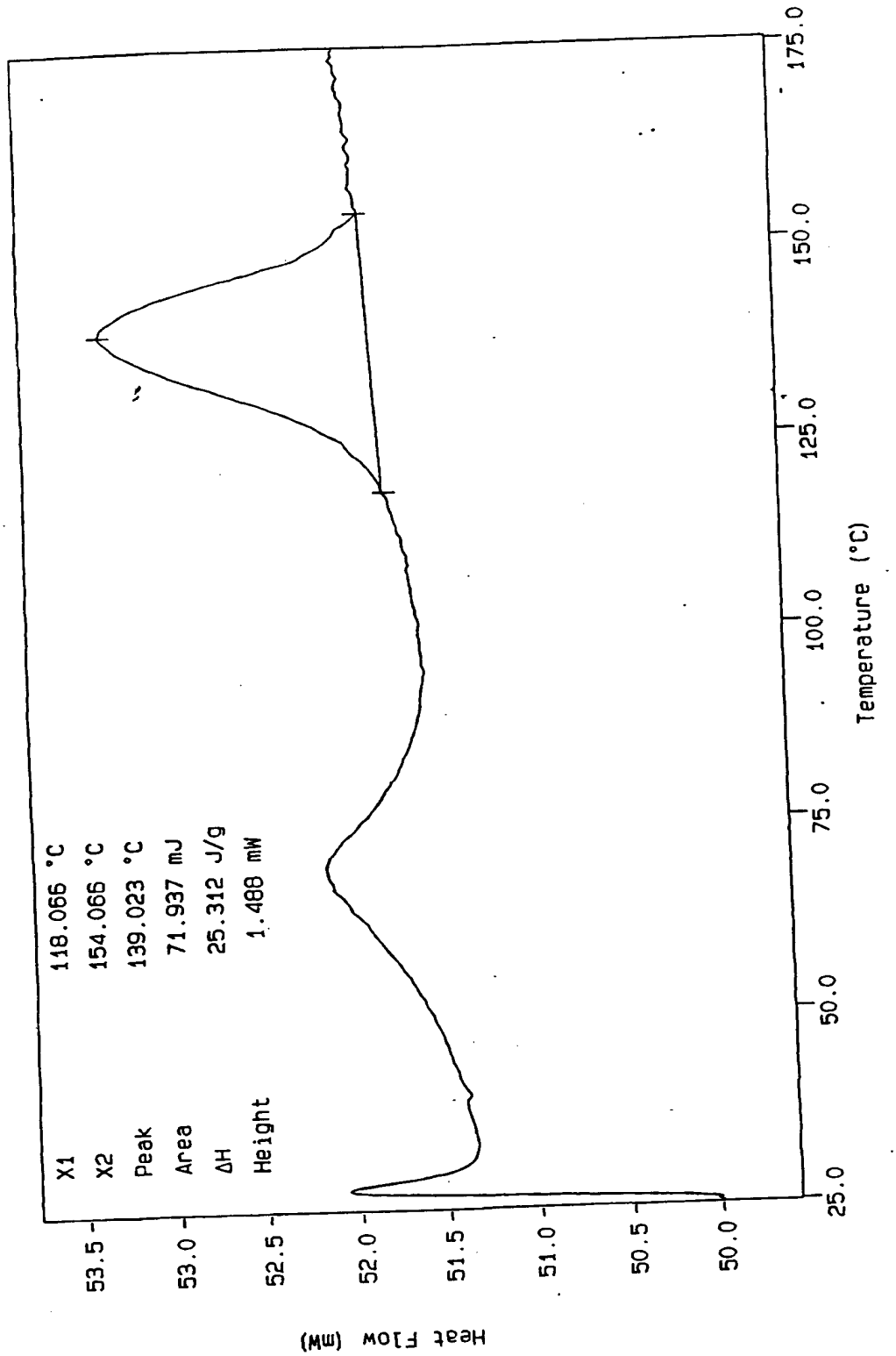


Figure 30 RASE64 indomethacin:PVP DSC scan

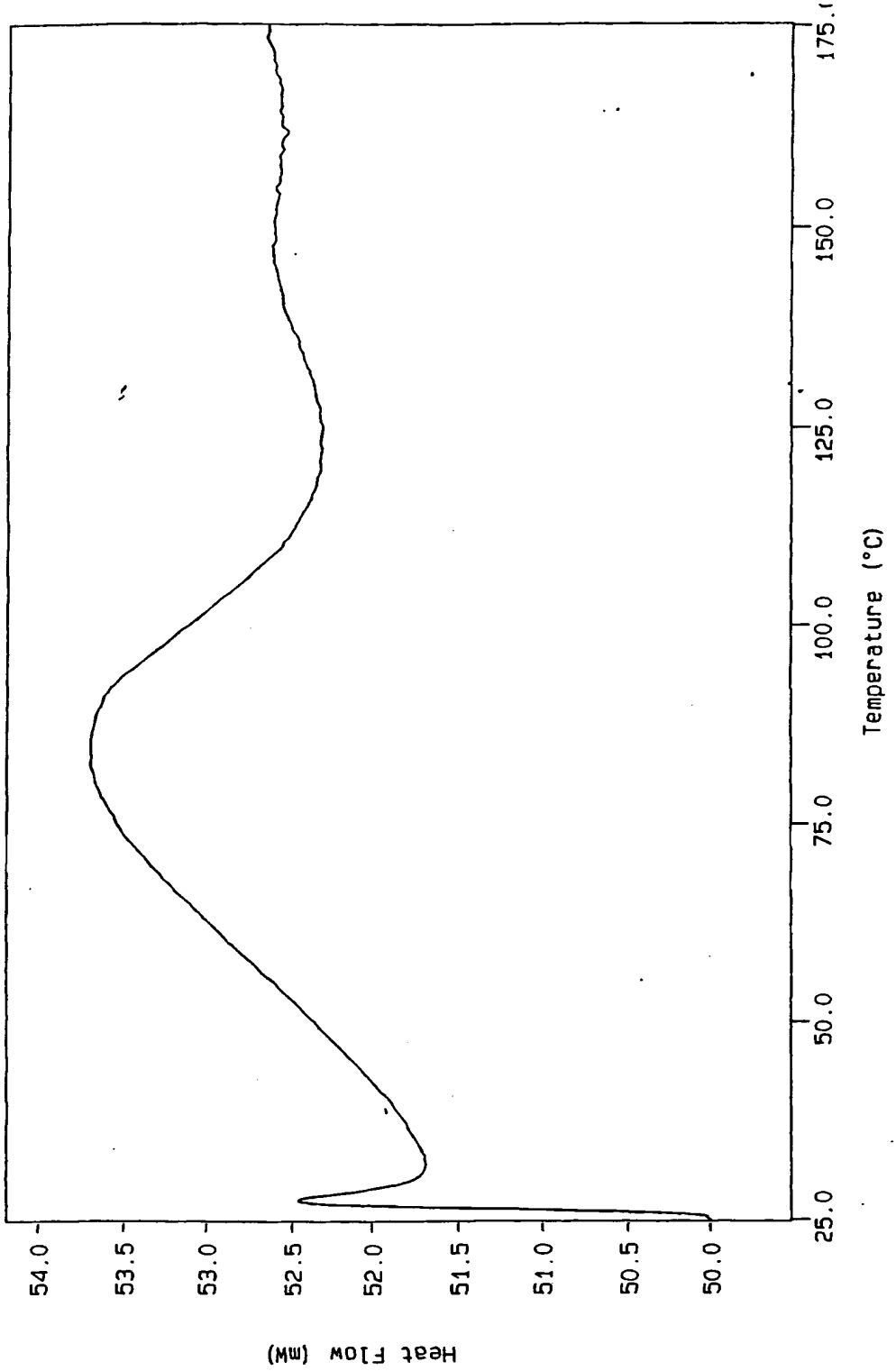


Figure 31 RASE70 indomethacin:PVP initial DSC scan

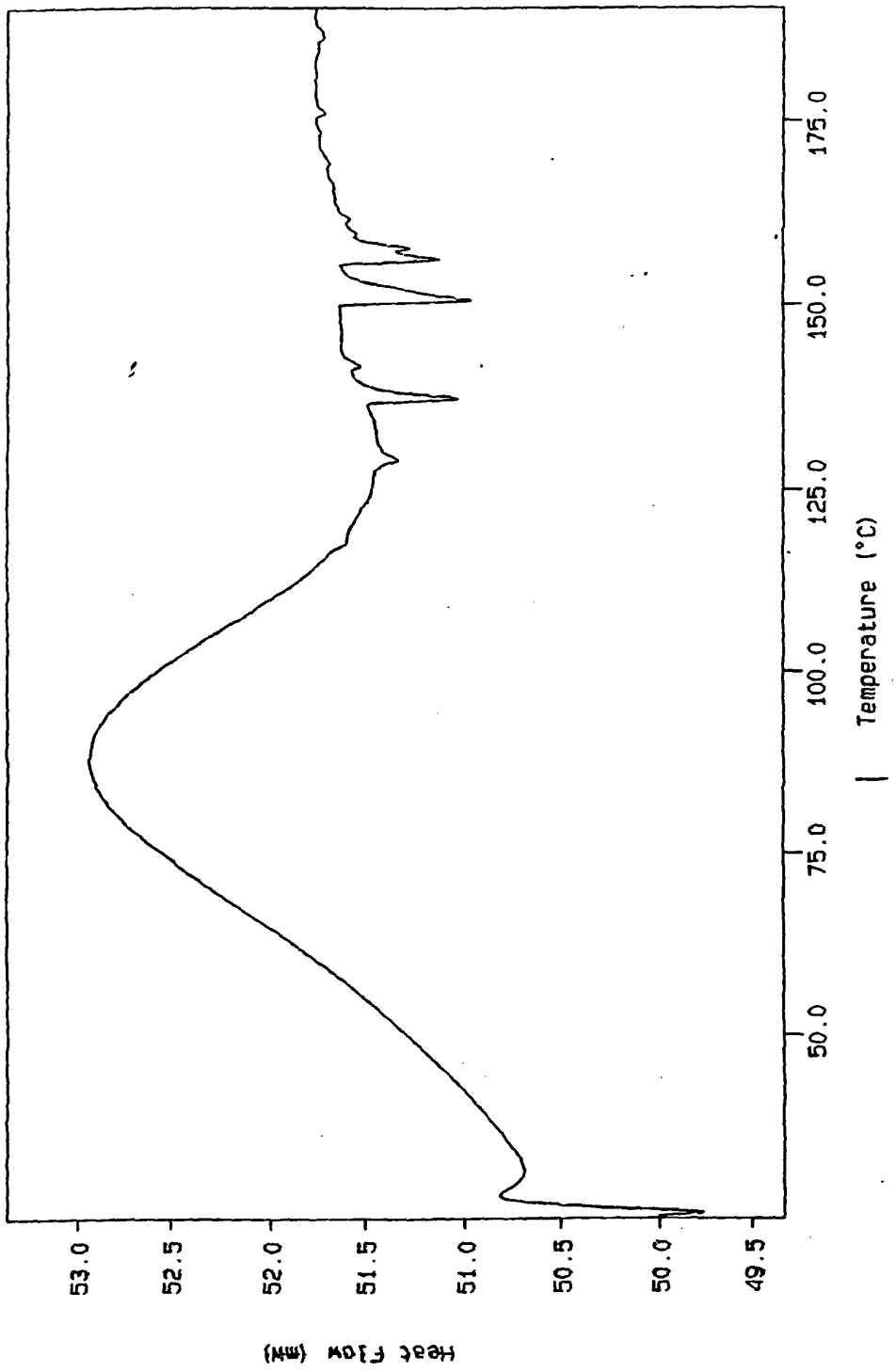


Figure 32 RASE70 indomethacin:PVP 12 month DSC scan

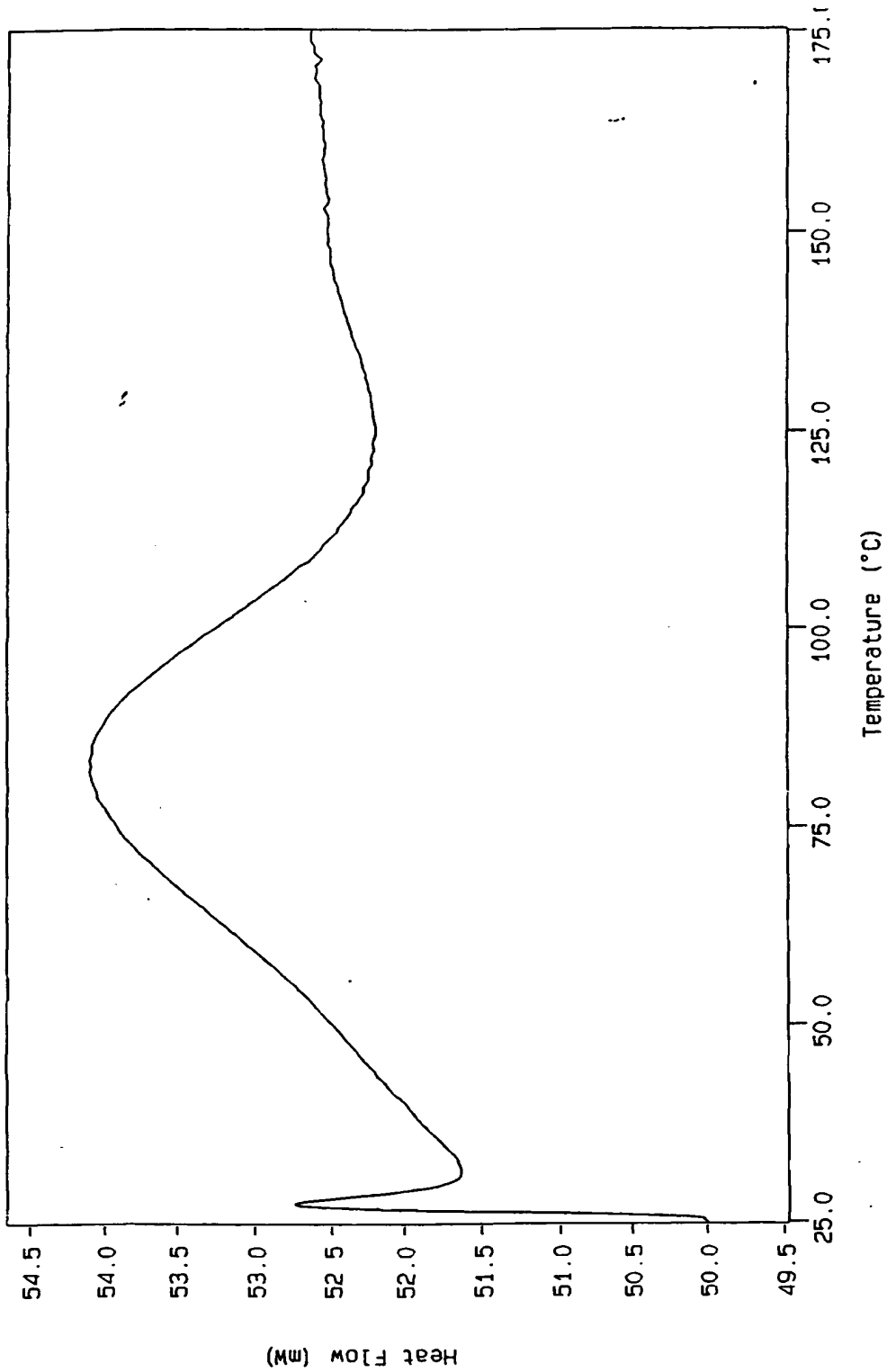


Figure 33 RASE69 indomethacin:PVP initial DSC scan

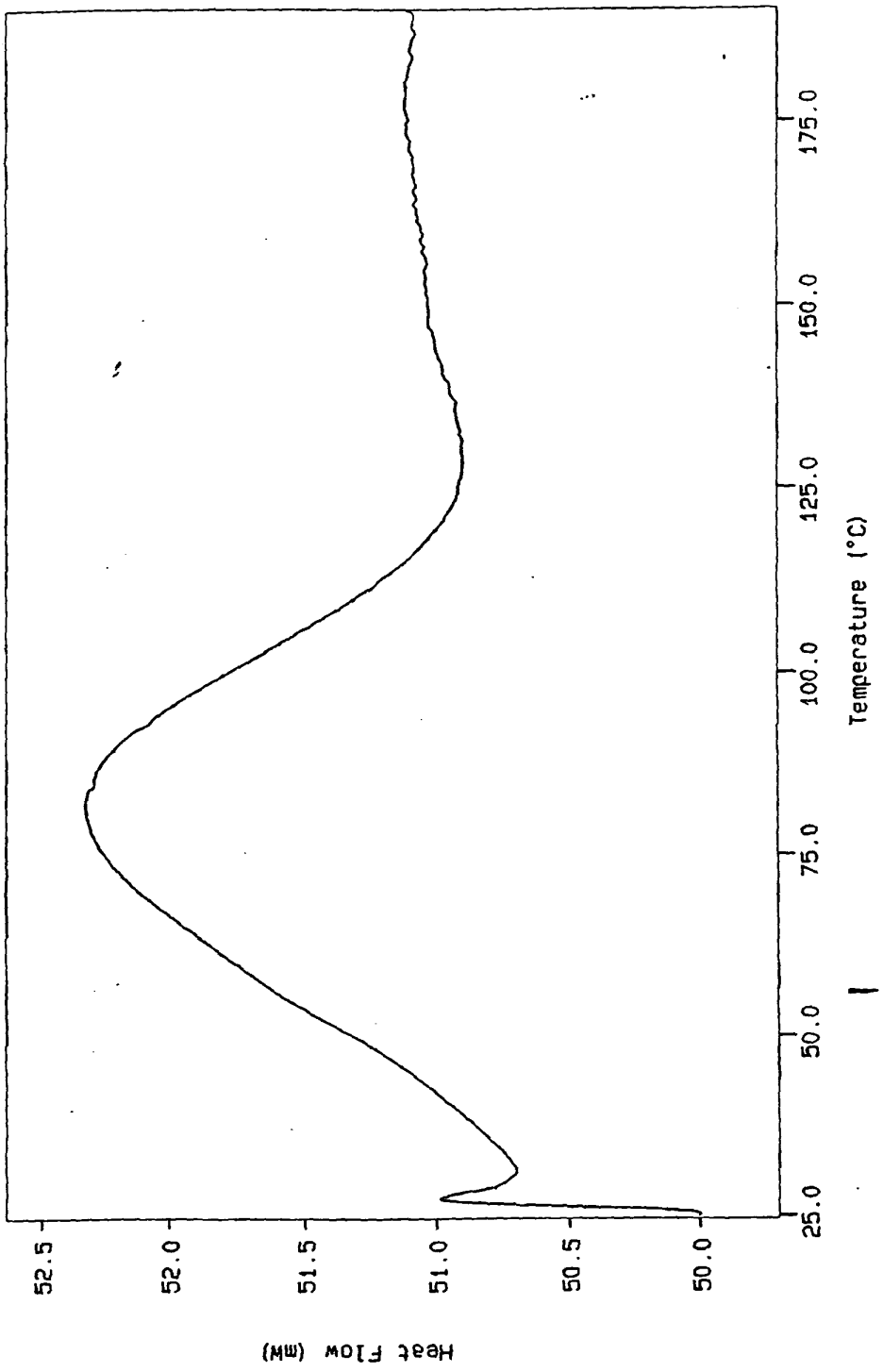


Figure 34 RASE69 indomethacin:PVP 12 month DSC scan

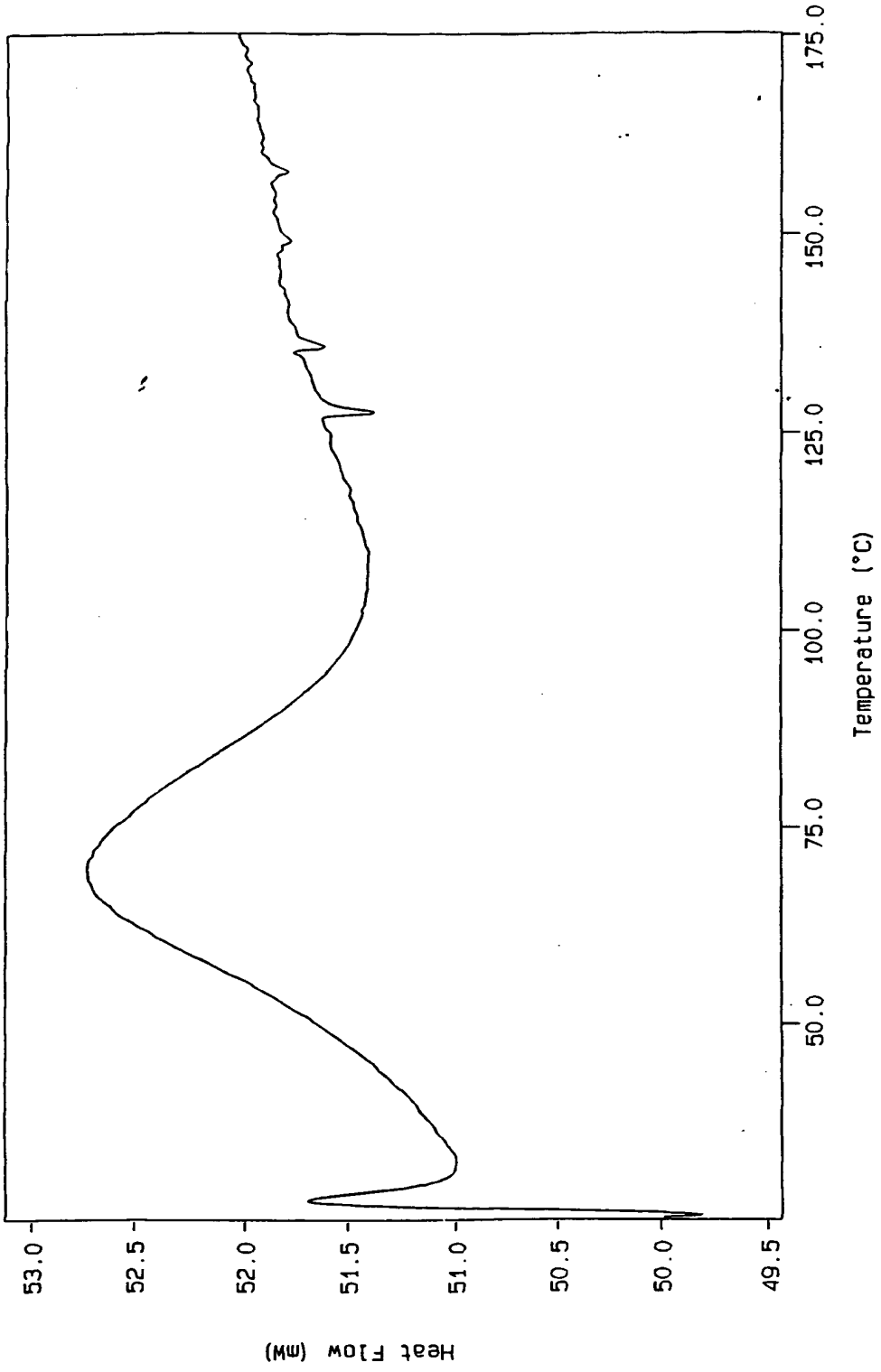


Figure 35 RASE62 indomethacin:PVP initial DSC scan

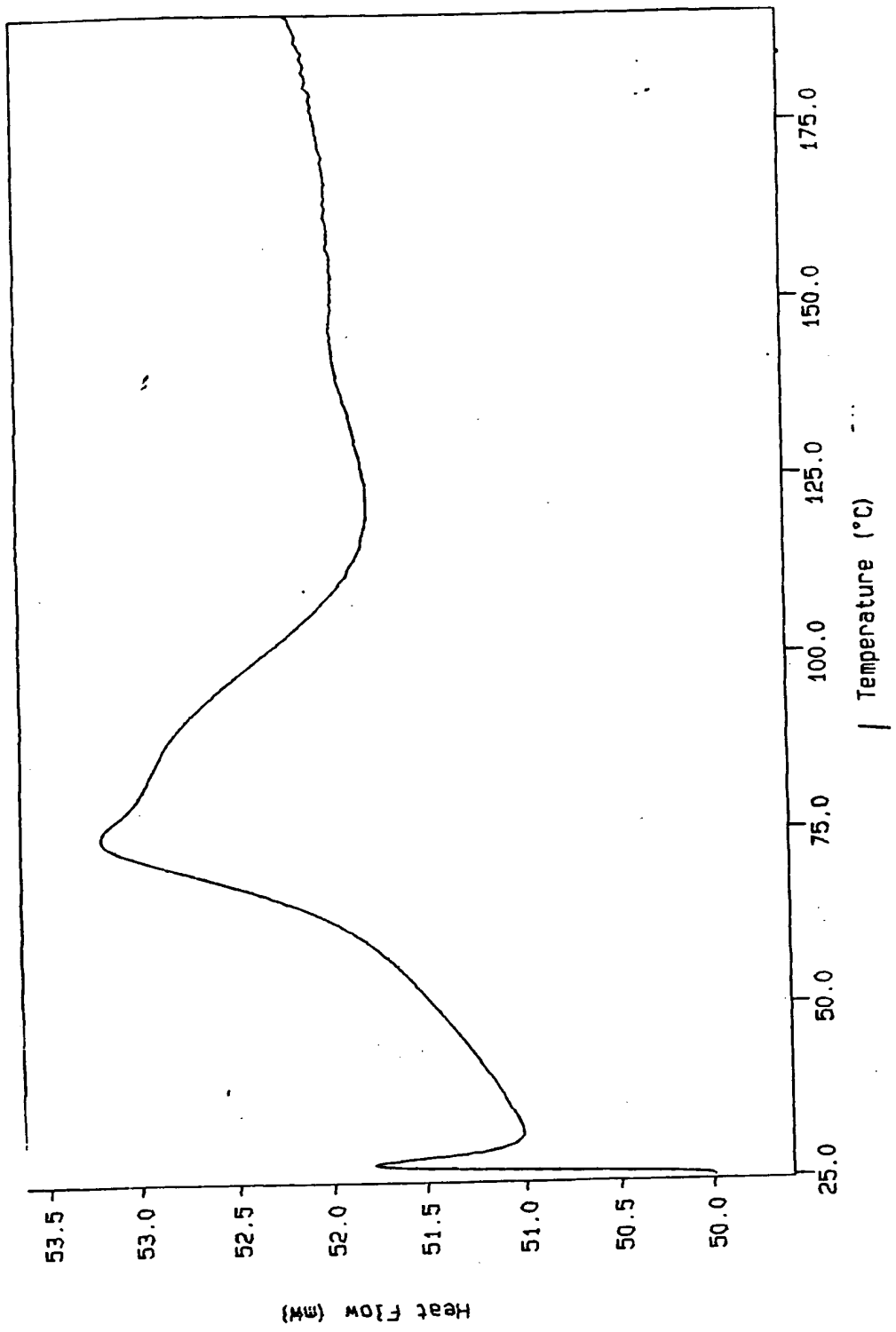


Figure 36 RASE62 indomethacin:PVP 12 month DSC scan

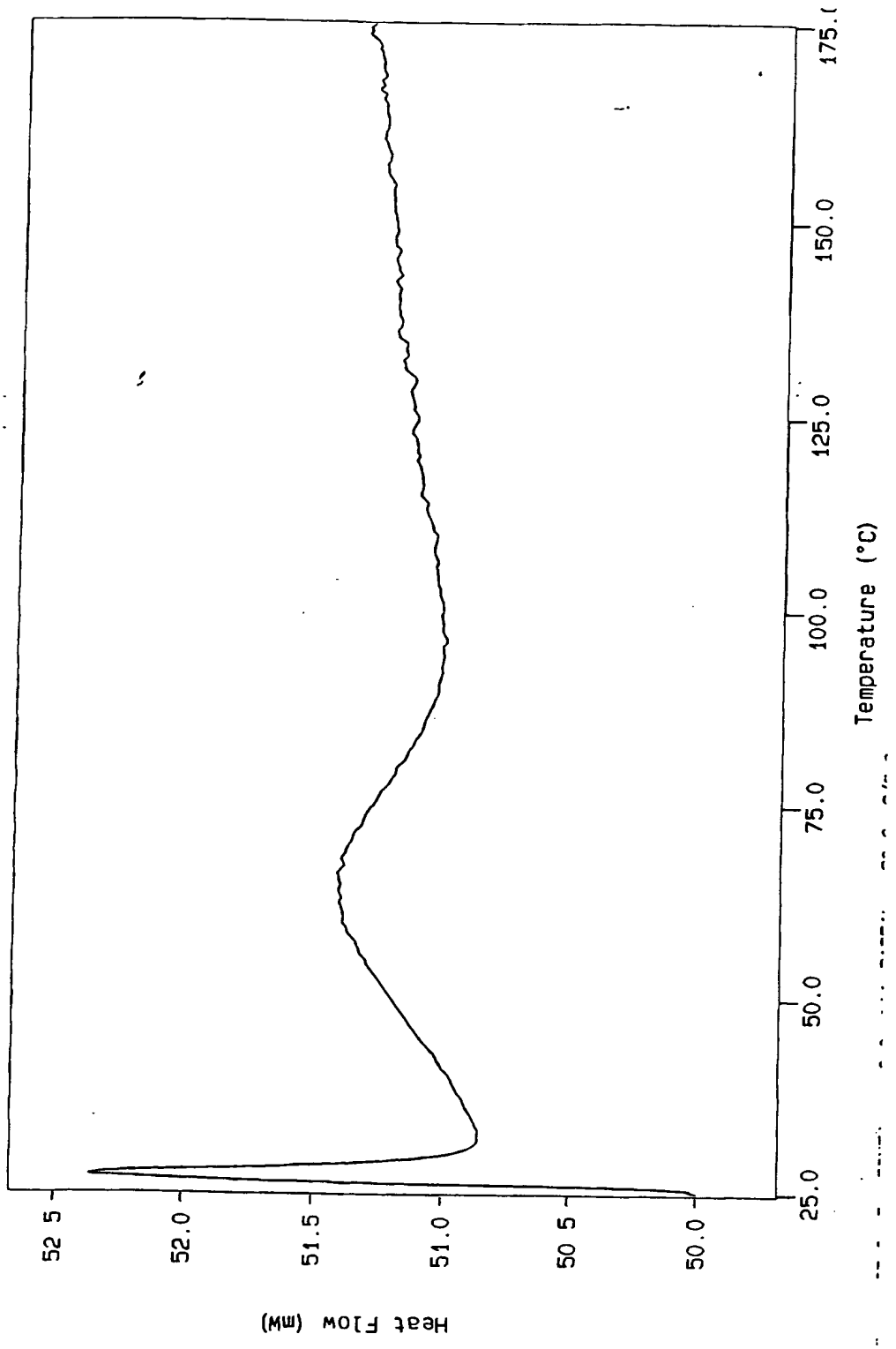


Figure 37 RASE66 indomethacin:PVP initial DSC scan

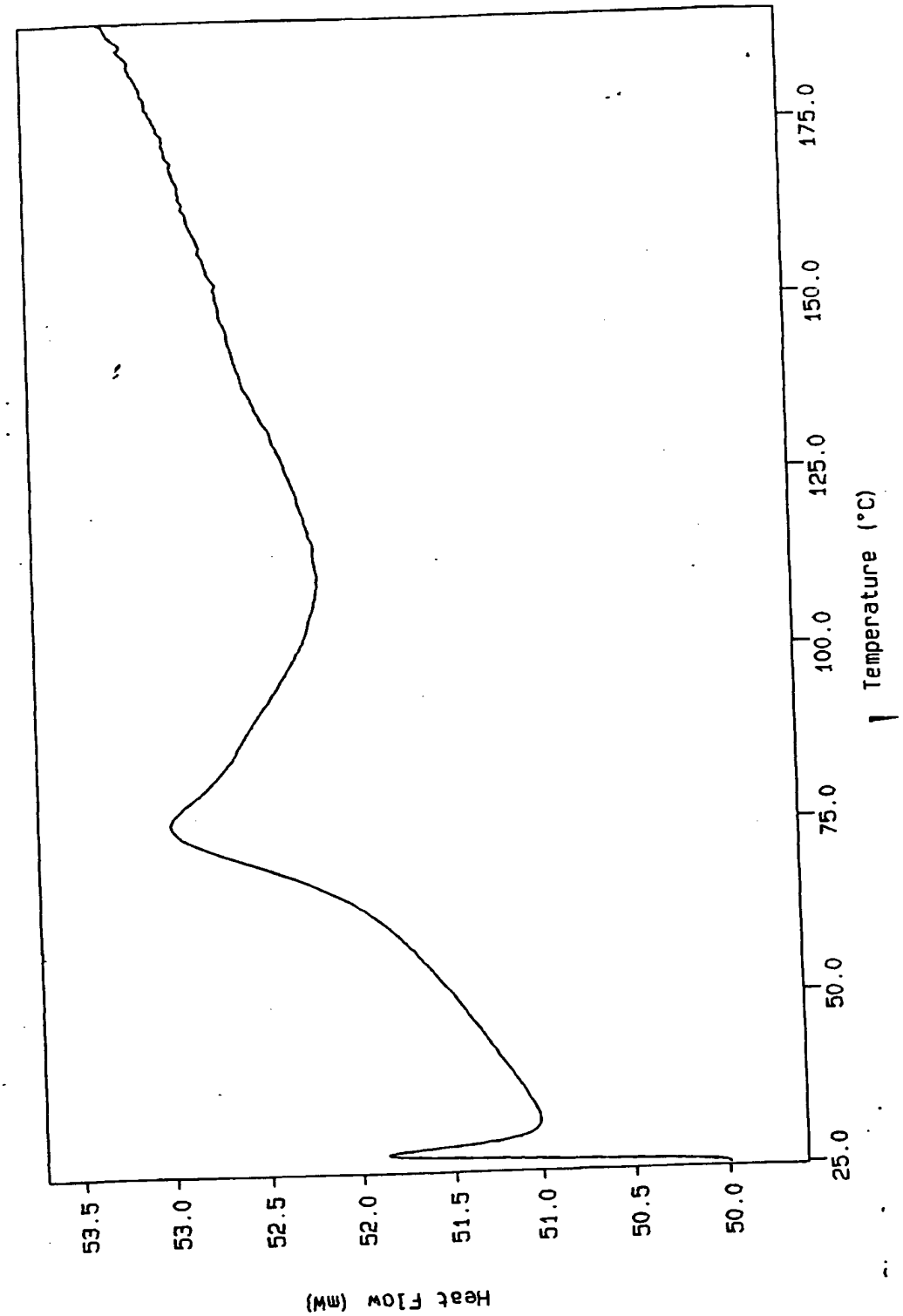


Figure 38 RASE66 indomethacin:PVP 12 month DSC scan

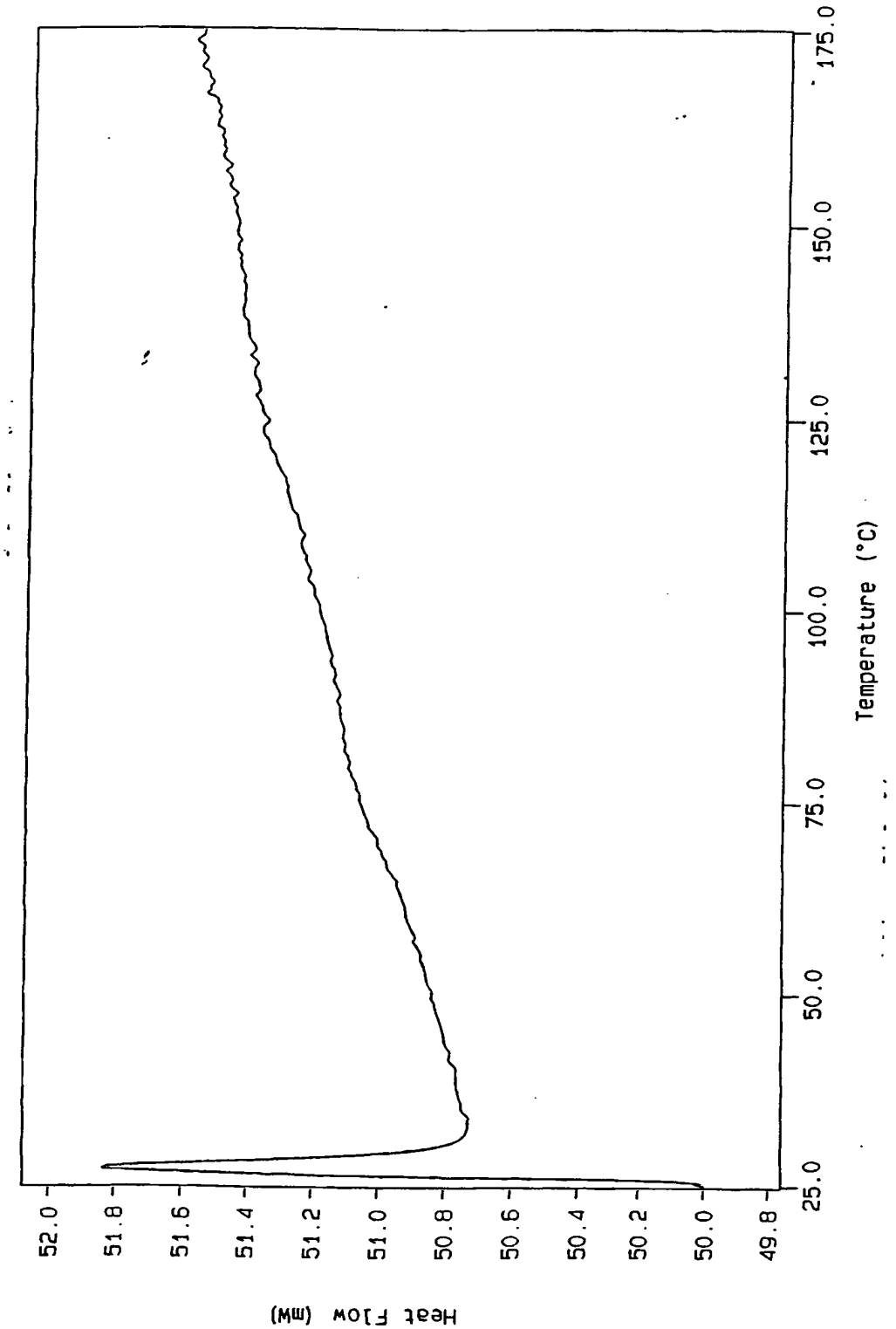


Figure 39 RASE63 indomethacin:PVP initial DSC scan

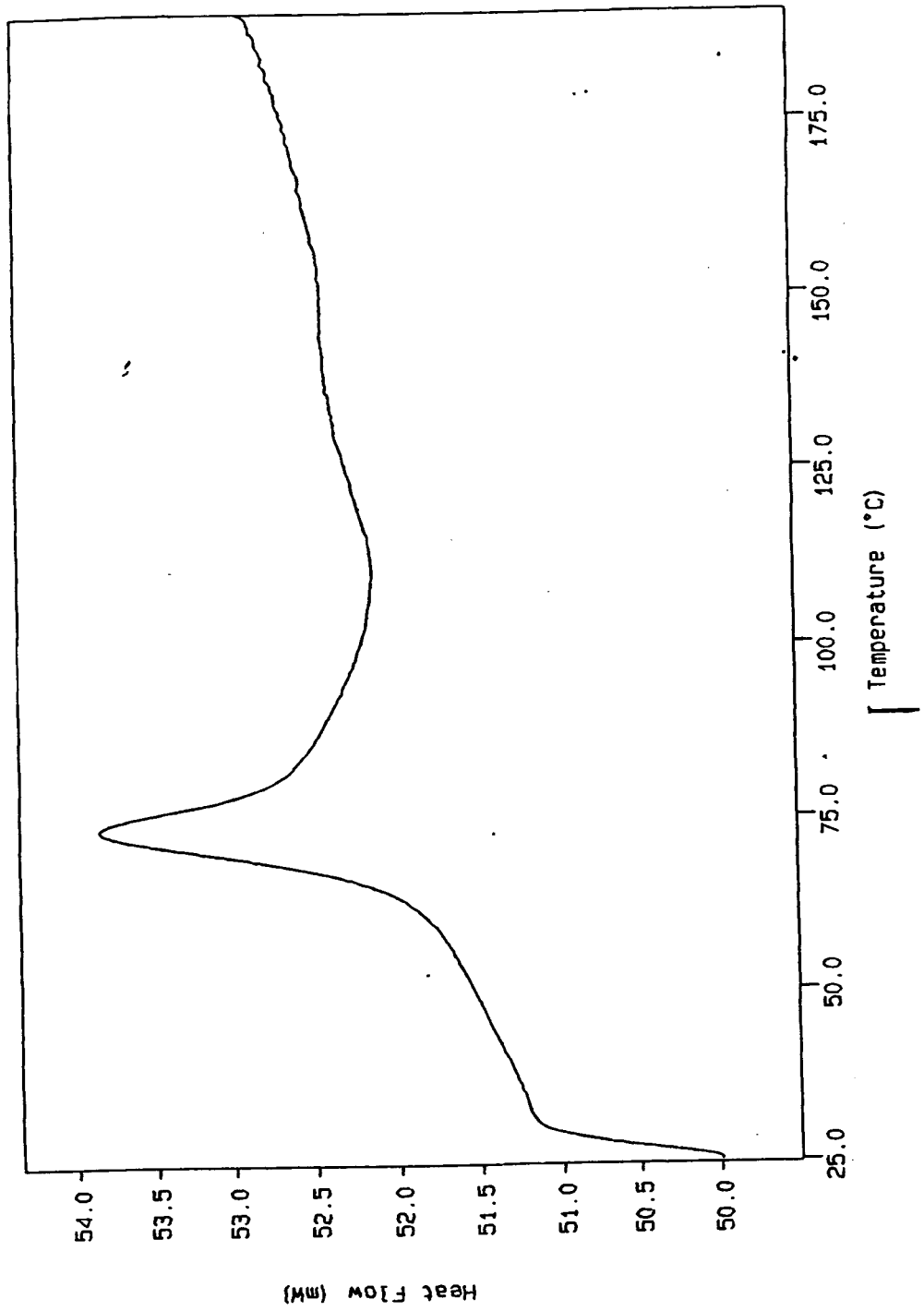


Figure 40 RASE63 indomethacin:PVP 12 month DSC scan

Figure ५१ Calculated values of $(\delta^d_{s-} \delta^p_s)$ plotted against X for drug:EC systems

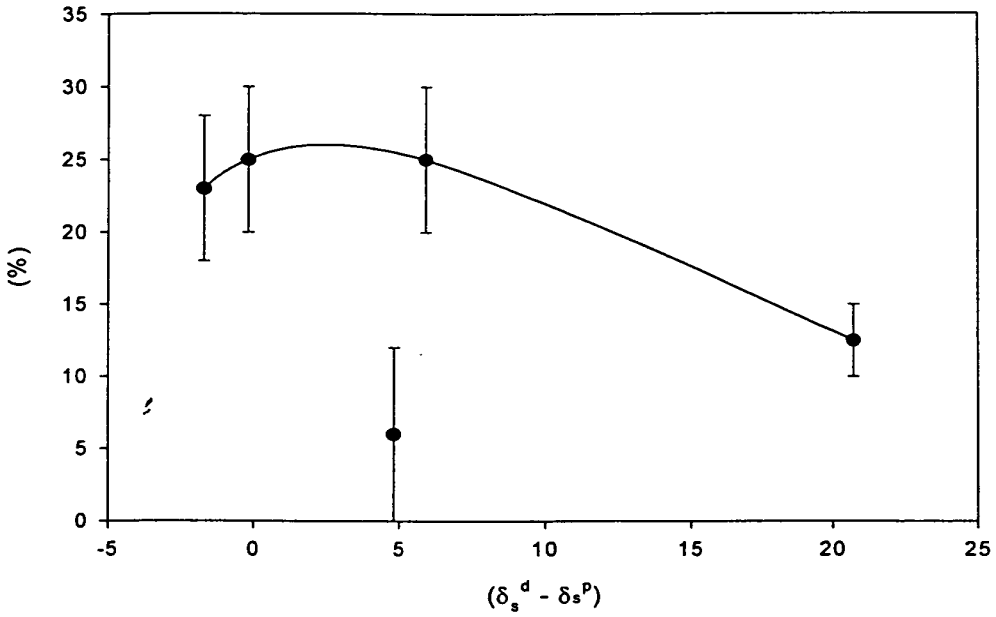
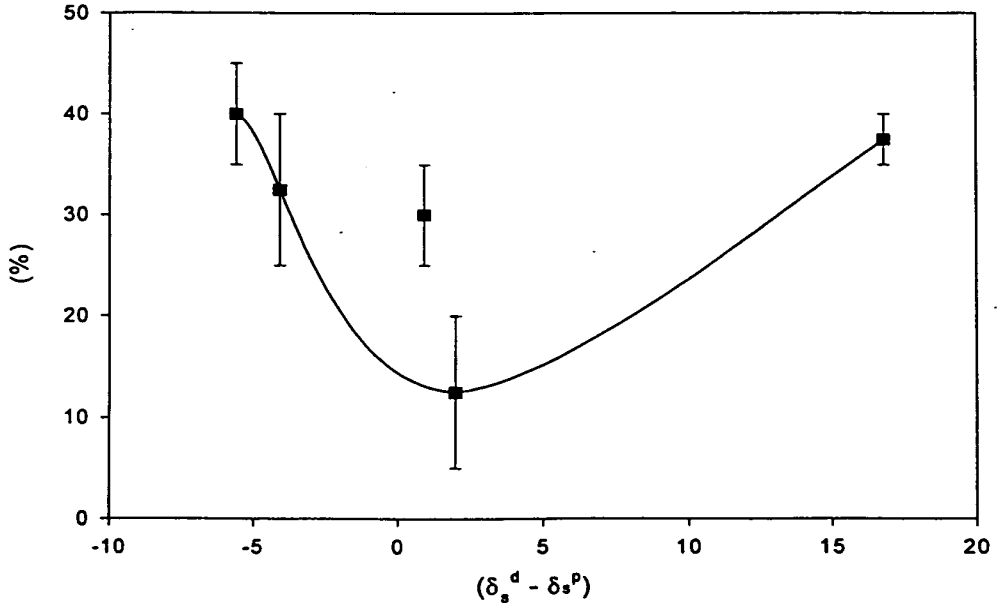


Figure ५२ Calculated values of $(\delta^d_{s-} \delta^p_s)$ plotted against X for drug:HPMC systems



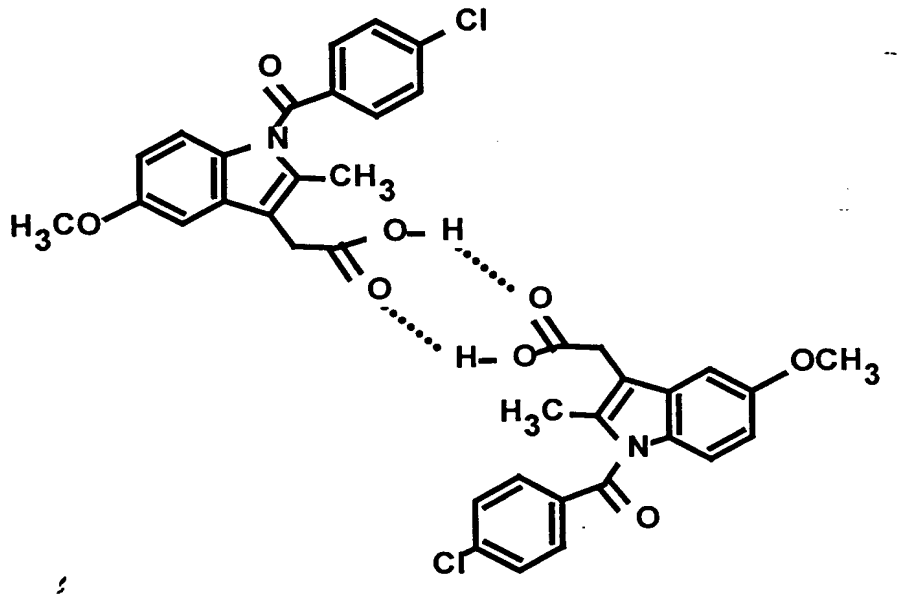
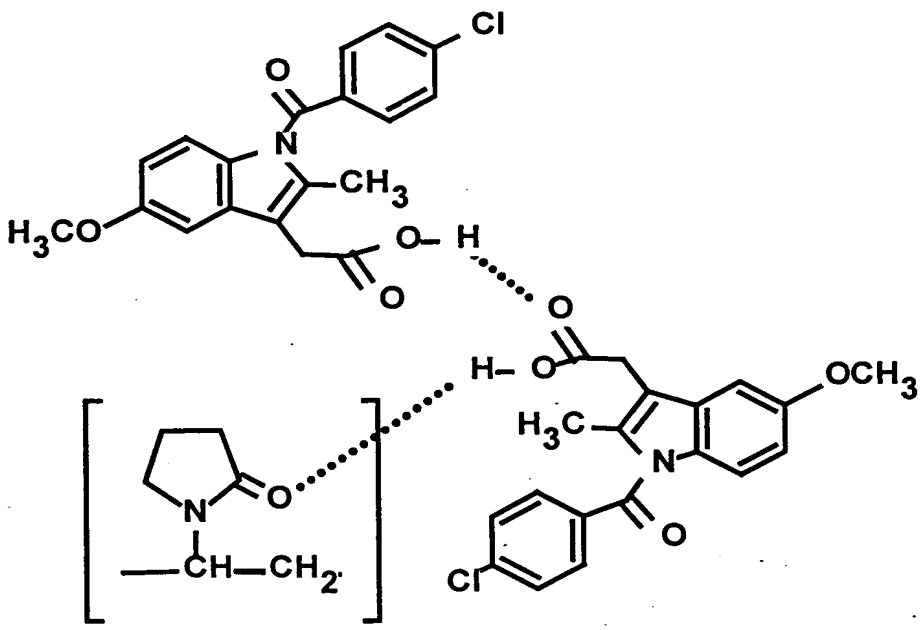


Figure 43 Cyclic dimer structure of the γ-indomethacin polymorph



PVP

Figure 44 Effect of PVP on γ-indomethacin hydrogen bonding